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The Management of Variceal Bleeding: Past, Present and Future

David C. Wolf, M.D.

Abstract

The basic principles of managing variceal bleeding have changed little in the last fifty years. Fluid resuscitation, efforts to induce intra-variceal thrombosis, and treatments to reduce portal pressures remain the keys to successful therapy. However, the last decade has seen the introduction of new modalities which have improved treatment efficacy and safety. Octreotide and, at many institutions, terlipressin have supplanted intravenous vasopressin as acute pharmacologic therapy for variceal bleeding. Endoscopic management of variceal bleeding now includes endoscopic variceal ligation in addition to the widely practiced endoscopic sclerotherapy. Placement of transjugular intrahepatic portosystemic shunts has been proven to be a reliable means of emergently inducing a reduction in portal pressure and stopping variceal hemorrhage. In the out-patient setting, therapy with non-selective ß-blockers, often coupled with oral nitrates, is increasingly accepted as a means of improving portal hypertension and reducing a patient's risk of first hemorrhage or recurrent variceal bleed.

This review focuses on the history and evolution of management strategies for variceal bleeding, discusses the physiologic basis for each type of therapy, summarizes current treatment approaches, and addresses recent developments in the field. **Key Words:** Varices, variceal bleeding, gastrointestinal bleeding, portal hypertension, octreotide, sclerotherapy, endoscopic variceal ligation, TIPS, shunt surgery, review.

Physiology of Portal Hypertension

The formation of esophageal and gastric varices is a common sequela of portal hypertension. Portal hypertension is defined as elevated pressure within some portion of the portal venous system. Both portal hypertension and variceal bleeding have been associated with a wide variety of diseases, ranging from Budd-Chiari syndrome to malignant splenic vein thrombosis to cirrhosis. In patients with cirrhosis, increased splanchnic arterial blood flow and, accordingly, increased splanchnic venous inflow into the liver, play important contributing roles. Putative splanchnic vasodilators include: glucagon, vasoactive intestinal peptide, substance P, prostacyclin, bile acids, TNF-α and nitric oxide (1). Another contributing factor to the development of portal hypertension in cirrhosis is elevated resistance across the sinusoidal vascular bed of the liver. Factors which increase resistance to blood flow include: disruption of hepatic architecture and compression of hepatic venules by regenerating nodules; increased collagen deposition in the space of Disse; and increased intrahepatic levels of locally acting vasoconstricting chemicals. Amelioration of these factors in the cirrhotic patient can reduce portal pressure and stop or prevent variceal bleeding.

Varices form when portal hypertension causes dilation of portosystemic collateral vessels. Blood may be shunted from the portal circulation into the systemic circulation. In the case of esophageal and gastric varices, increased blood flow is noted in the azygos vein, on account of hepatofugal flow in the left gastric vein (or coronary vein) and short gastric veins (which collater-

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alize with the splenic vein). Groszmann's group at Yale and others have shown that varices do not arise in mild portal hypertension. Once the hepatic venous pressure gradient (the difference in pressure between the portal vein and the hepatic vein) exceeds 12 mm Hg, varices may form in the esophagus and stomach (2, 3). Reduction of portal pressures below this threshold, whether it be by pharmacologic or by surgical means, virtually eliminates the patient's risk for variceal hemorrhage.

In the esophagus, varices first arise at the gastroesophageal junction. Local factors, including the amount of supporting esophageal tissue, may have an impact upon the diameter to which a superficial varix may dilate. Large varices, measured at more than 5 mm in diameter, have a greater predisposition to spontaneously rupture than small varices (4). This, presumably, is a result of the increase in wall tension which occurs when varices increase in size (5). It is now well appreciated that varices do not erode. Indeed, gastroesophageal reflux does not appear to play a role in inducing variceal hemorrhage. Rather, variceal bleeding appears to be an explosive event (6).

Epidemiology of Variceal Bleeding

Varices are identified in about 30% of patients with well-compensated cirrhosis and in 60% of patients with decompensated cirrhosis (7). Small varices are at low risk of hemorrhage. It is estimated that varices will increase in size from "small" to "large" at a rate of 10–20% per year (7, 8). Variceal bleeding occurs at a rate of 10–20% per year, when all patients with varices are considered (9–11), but rises to more than 20–30% per year in patients with large varices (4, 11). This statistic takes on added importance with the knowledge that bleeding from varices is the cause of more than one quarter of all deaths in patients with cirrhosis (12).

Initial variceal bleeding stops spontaneously in 60–70% of patients (13, 14). However, 17–42% of patients with early hemostasis will rebleed within 5–10 days of their initial hemorrhage (15, 16). Variceal bleeding and early rebleeding are associated with a high mortality rate, estimated at about 40% (see below). Exsanguinating hemorrhage itself is responsible for about 60% of deaths which occur within 6 weeks of the initial hemorrhage. Recurrent bleeding is responsible for about 40% of late deaths (13). Progressive liver failure and hepatorenal syndrome frequently complicate variceal bleeding and may result in death. These conditions are presumably precipitated by a state of decreased hepatic and renal blood flow. Thus, it is imperative that intravascular volume be maintained by aggressive resuscitation with fluid and blood products. However, care must be taken to avoid over-transfusion (above a hematocrit of 30%), as this may acutely worsen portal hypertension. Sepsis and, in patients with ascites, spontaneous bacterial peritonitis are frequently seen in the setting of variceal bleeding. Increasingly, there is interest in using selective intestinal decontamination (e.g., with norfloxacin 400 mg per nasogastric tube twice daily) in an effort to prevent serious infection in cirrhotic patients who develop gastrointestinal hemorrhage (17).

It has long been known that both early and late mortality following variceal bleeding are closely tied to a patient's Child class at time of onset of bleeding (18–22). Table 1, derived from Pugh et al. (19), has been modified to include the international normalized ration (INR) readings for the prothrombin time. Patients with well-compensated liver disease receive a Child class A status. Patients who suffer from some degree of hepatic encephalopathy, ascites, jaundice or hepatic synthetic dysfunction, as marked by a depressed serum albumin or an elevated prothrombin time, have a Child class B or C status. Following variceal bleeding, 30-day mortality rates have been estimated at: less than 10% for Child class A, 30% for Child class B, and more

TABLE 1
Child Class

Clinical and biochemical measurements	Points accorded		
	1	**2**	**3**
Encephalopathy	None	Stage 1 and 2	Stage 3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	< 2	2–3	> 3
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
Prothrombin time (seconds prolonged)	< 4	4–6	> 6
INR	< 1.7	1.7–2.3	> 2.3
Point modification for primary biliary cirrhosis or primary sclerosing cholangitis:			
Bilirubin (mg/dL):	< 4	4–10	> 10
Class A: 5–6 points			
Class B: 7–9 points			
Class C: 10–15 points.			

Modified from Pugh RNH, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60:646–649 (19), and reproduced with the permission of the editors of the British Journal of Surgery.

than 45% for Child class C (20). For patients who survive the initial variceal bleed, the one-year mortality rate is estimated to be 50% when all patients with cirrhosis are considered (13). When segregated by severity of liver disease, one-year mortality rates are estimated at: 24% for Child class A, 48% for Child class B, and 65 – 89% for Child class C (20, 21).

Treatment to Reduce Intrahepatic Resistance

Since the 1940s, clinical investigators have recognized that reduction of portal pressure may abate active variceal bleeding and help prevent repeat bleeds. From a physiologic perspective, each treatment strategy has a primary mechanism of action: reduction of intrahepatic vascular resistance, reduction of portal venous inflow, or "non-physiologic" obliteration of esophageal varices. Both portocaval shunt surgery and its angiographic equivalent, the transjugular intrahepatic portosystemic shunt (TIPS), decrease portal pressure by bypassing the high-resistance sinusoidal bed of the cirrhotic liver (see below). Nitrates, administered either intravenously or orally, also help overcome sinusoidal resistance. Indeed, nitrates appear to relax the smooth muscle contraction of the myofibroblast cells (also known as stellate or Ito cells) which line the hepatic sinusoid. Furthermore, they appear to reduce portal-collateral resistance in other vascular beds. Nitrates are not effective as single agents in the control of acute variceal bleeding. However, they are often used in combination with other drugs. In the mid 1980s, it was demonstrated that nitroglycerin, administered intravenously at a rate of 50 µg/min, significantly improved the rate of control of variceal hemorrhage when added to a regimen of vasopressin (23). A decade later, many investigators showed that the addition of isosorbide-5-mononitrate to a regimen of propranolol or nadolol significantly improved portal hypertension (24) and increased the efficacy of oral β-blockers in preventing recurrent variceal bleeding (25, 26). Recently, nitrates were shown to be effective as single agents in the primary prophylaxis of variceal bleeding (27). The findings of this study require confirmation by additional investigations.

Treatment to Reduce Portal Venous Inflow

Over the last 40 years, and especially since the 1980s, it has been increasingly appreciated that a hyperdynamic circulation and increased portal venous inflow play major roles in the development of portal hypertension (1). Coincident with advances in understanding the basis for portal hypertension, there has been increased clinical investigation of pharmacologic strategies to reduce portal venous inflow.

"Posterior pituitary extract" was first administered to patients with bleeding esophageal varices in the 1950s and 1960s (28 – 30). Additional trials using arginine vasopressin, lysine vasopressin and the synthetic Pitressin were conducted from the mid-1970s to the late 1980s. Vasopressin binds to the V_1 receptor of vascular smooth muscle cells and it induces vasoconstriction in the mesenteric arterial circulation. As a result, there is decreased portal venous inflow and a subsequent reduction in portal pressure. Disparate studies have demonstrated that acute variceal bleeding is controlled in 29 – 71% of cases treated with vasopressin alone, and in 45 – 73% of cases when vasopressin is combined with nitroglycerin. Most studies demonstrate the superiority of vasopressin over placebo, and the superiority of vasopressin plus nitroglycerin over vasopressin alone (7).

Typical vasopressin dosing is 0.4 units per minute intravenously, used in combination with nitroglycerin 50 µg per minute intravenously. Treatment with vasopressin and nitroglycerin is tapered once bleeding has stopped and the patient no longer has an ongoing need for blood transfusion. If bleeding does not cease, the vasopressin dose may be increased to as high as 1.0 units per minute. However, higher doses are associated with increased side effects, including myocardial and gastrointestinal ischemia. The incidence of these severe side effects is reduced by co-administration with nitroglycerin. The efficacy and safety of vasopressin are not improved by direct infusion into the superior mesenteric artery (31).

Triglycyl-lysine vasopressin, also known as terlipressin, was first used in clinical trials in the late 1970s. However, its use only became popular in the early 1990s. Although the parent drug has no vasoactive properties, it is converted to the vasoactive lysine vasopressin after its terminal glycine residue is cleaved off *in vivo*. This results in the "slow release" of a vasoactive chemical. Terlipressin's theoretical advantages over vasopressin include: the convenience of bolus administration as opposed to continuous intravenous infusion; the drug's decreased cardiotoxicity; and its ability to control up to 70% of variceal hemorrhages. However, there have been few clinical trials using terlipressin (32). This may be due, in part, to other drugs, somatostatin and octreotide, which have attracted considerably more clinical attention in the 1990s (33 – 39).

Octreotide is the synthetic octapeptide analog of somatostatin, a 14 amino acid hormone. Somatostatin has a half life of one minute, which necessitates administration via continuous infusion. Octreotide, with a half life of 10–22 minutes, is also administered by continuous infusion but, in some circumstances, is given subcutaneously. Although neither drug appears to have direct vasoconstrictive properties, both were recognized in the early 1980s to decrease splanchnic arterial blood flow, with a subsequent decrease in portal inflow. Their mechanism of action is believed to be due to inhibition of vasodilatory gastrointestinal peptides, including: glucagon, vasoactive intestinal peptide, calcitonin gene related peptide, and substance P (32). Although their effect on reducing portal pressure is variable, somatostatin and octreotide consistently reduce azygos blood flow (33). Intravenous administration of somatostatin (typically at doses of 250 µg/hr, after bolus administration of 250 µg) and octreotide (typically at doses of 50 µg/hr) have controlled variceal bleeding in 40–90% of cases (34–37). A number of studies have shown the efficacy of somatostatin (35, 37) and octreotide (36) to be equivalent to endoscopic sclerotherapy (ES). In general, treatment is continued for 2–5 days. Although bolus administration of octreotide has been shown to reduce cardiac output and increase pulmonary capillary wedge pressure in controlled settings, the clinical impact of this is unclear (38). Somatostatin and octreotide are associated with few other side effects. Their ease of administration, their safety and their efficacy lead me to recommend the use of somatostatin or octreotide as soon as variceal bleeding is suspected. However, I am not yet prepared to recommend treatment with either drug as an alternative to emergent therapeutic endoscopy. An area for future exploration is the use of subcutaneous octreotide in the secondary prophylaxis of variceal bleeding. One preliminary study demonstrates that octreotide 100 µg administered subcutaneously every 8 hours increases the efficacy of ES in the prevention of variceal rebleeding (39) whereas a more recent work suggests this medication is ineffective (40). Other authors postulate that higher doses of octreotide, up to 500 µg administered subcutaneously every 8 hours, may be needed in order to maintain the plasma levels achieved by a 25 µg/h intravenous infusion, an octreotide dose which has been successful at stopping variceal bleeding (41).

The ability of β-adrenergic blockers to decrease splanchnic blood flow has been known since the 1960s (42). Non-selective β-blockers like propranolol and nadolol are particularly effective in reducing portal pressures in cirrhotics. β1 blockade reduces cardiac output. β2 blockade produces a state of unopposed α-adrenergic stimulation, with resulting constriction of both the peripheral and splanchnic circulations. The subsequent reduction in portal venous inflow and portal pressure has a major clinical impact. Although β-blocker therapy does not play a role in the patient with acutely bleeding varices, a meta-analysis of heterogeneous studies comparing propranolol or nadolol to placebo showed a reduction in the relative risk of recurrent variceal bleeding (pooled odds ratio = 0.40, 95% confidence interval = 0.30–0.54) (7). Given the safety and low cost of β-blocker therapy, we routinely recommend it as secondary prophylaxis against variceal bleeding. The data is even more compelling vis-à-vis the use of β-blockers as primary prophylaxis. Meta-analysis demonstrates a significant decreased relative risk for initial variceal bleeding in patients with asymptomatic esophageal varices who are treated with a β-blocker (pooled odds ratio = 0.54, 95% confidence interval = 0.39–0.74). However, there was not a significant reduction in the mortality rate (pooled odds ratio = 0.75, 95% confidence interval = 0.57–1.06) (7). It has been estimated that 9–11 patients must be treated with β-blockers in order to prevent one bleeding event (11). However, the safety of treatment and the potential catastrophic nature of variceal bleeding argue strongly in favor of β-blocker primary prophylaxis.

Therapeutic Endoscopy: A "Non-Physiologic" Approach to Variceal Bleeding

The goal of therapeutic endoscopy is to stop acute variceal bleeding by creating an intravariceal thrombus. Repeated procedures may ultimately induce variceal obliteration. Two techniques are in common use: endoscopic sclerotherapy (ES) and endoscopic variceal ligation (EVL). Neither procedure produces a reduction in portal pressure. In fact, the successful obliteration of varices may actually increase portal pressures in some patients. Although portal hypertension is not ameliorated, both ES and EVL are highly effective in treating acute variceal bleeding and have acceptable complication rates.

In ES, an irritant solution (e.g., sodium morrhuate, ethanolamine or polidocanol) or a dehydrating chemical (e.g., sodium tetradecyl sulfate) is injected into an esophageal varix or its adjacent supporting tissues. The goal is the acute induction of vascular spasm, with subsequent development of intravariceal thrombosis, intimal thickening and perivenous fibrosis (43). ES, utilizing a rigid esophagoscope, was first reported by Crafoord and Frenckner in 1939 (44). Large esophageal varices were obliterated in a 16-year-old girl after a one-month course of quinine hydrochloride injections every other day. Two years later, Moersch (45) used repeated injections of sodium morrhuate to obliterate esophageal varices, with prevention of rebleeding in 6 of 11 patients under treatment. However, enthusiasm for ES waned as surgeons gained increasing experience with portocaval shunt surgery. A number of large series of patients undergoing successful ES, all employing rigid esophagoscopes, was reported in the 1970s (46–48). This, and the advent of flexible fiberoptic endoscopy in the mid-1970s, spurred interest in adapting this new technology for performance of ES. The first published report of ES utilizing a flexible fiberoptic endoscope appeared in 1979 (49). By the mid-1980s, it was recognized that ES could achieve early hemostasis in up to 95% of patients suffering from variceal bleeding. Controlled trials demonstrated that ES was consistently more effective than treatment with intravenous vasopressin (7). Accordingly, ES became the "gold standard" for the emergent treatment of bleeding esophageal varices.

Repeated application of ES or EVL, over a period of weeks to months, can obliterate varices and prevent rebleeding. When no attempt is made to obliterate varices, about 75% of patients eventually rebleed. When long-term ES is attempted, varices are obliterated in about 50% of patients (reported as a range of 27–85% by Laine and Cook) (50). Varices redevelop in 28–60% of patients following obliteration, with rebleeding in 4–44% of these cases (51, 52). These bleeds are usually less severe than the index hemorrhage. In most cases, rebleeding is controlled by reapplication of ES. Further episodes of bleeding are usually prevented by performance of additional ES (53) or by adding β-blockers and nitrates to the patient's regimen. Patients who fail repeat ES and aggressive medical therapy will require TIPS or portocaval shunt surgery. It remains controversial as to whether successful obliteration of varices in patients following index variceal hemorrhage actually helps to improve long-term survival.

Esophageal sclerotherapy has a number of important problems. First, it usually takes 3–6 ES sessions to obliterate esophageal varices (50). ES is rarely successful in the emergent control of bleeding from large gastric varices. Furthermore, ES plays no role in treating the bleeding which may develop from portal hypertensive gastropathy. Finally, side effects and procedural complications are common, especially following treatment of the actively bleeding patient. The most common complications result from the development of post-sclerotherapy esophageal ulcers. Patients may experience chest pain or odynophagia in the early post-ES period. Bleeding from post-sclerotherapy ulcers is seen in 5–13% of patients (54). Encouragingly, bleeding is usually self-limited and stops without requiring endoscopic therapy or portal decompression. Post-sclerotherapy ulcers may also be complicated by esophageal dysmotility and esophageal stricturing, which are seen in 1.6–3% of patients. ES-induced strictures occasionally necessitate additional endoscopy to facilitate esophageal dilation (54). Sclerotherapy is known to worsen portal hypertensive gastropathy and increase the size of gastric varices seen at sites "upstream" from the level of variceal obstruction (55). Other important complications of ES include: esophageal perforation, estimated at an incidence of 0.5% per ES session; systemic infection; pleural effusion; aspiration pneumonia; adult respiratory distress syndrome; mediastinitis; and portal and mesenteric venous thrombosis (54). The mortality rate of ES, performed in the setting of acute variceal bleeding, has been estimated at 1–2% (56). Elective ES in the non-bleeding patient is believed to be considerably safer.

Endoscopic variceal ligation (EVL) is a promising alternative to ES. The technique is derived from a hemorrhoid banding procedure which was first introduced in 1963. Stiegmann and Goff (57) reported the first clinical experience with EVL in 1988. Although band ligating devices have evolved over the last decade, the basic principles of the procedure remain unchanged. A standard endoscope is outfitted with a special ligating chamber at its tip. After insertion of the endoscope, a varix is identified by the endoscopist and the varix is suctioned into the ligating chamber. By pulling a trip wire, the endoscopist releases an elastic "O" ring around the neck of the varix, creating a "polyp" (57). This results in the coagulative necrosis of the ensnared polyp, with eventual sloughing. Varices in the adjacent submucosa subsequently thrombose. In addition, acute inflammation in the superficial mucosa leads to the formation of shallow ulcers. As ulcers heal, granulation tissue forms and helps to obliterate variceal channels, without damage to the underlying muscularis (58).

The original band ligating device could only deploy one "O" ring at a time. As a result, the endoscopist needed to pass an endoscopic overtube into the esophagus to facilitate band deployment, removal of the endoscope, reloading of a new band, and reinsertion of the endoscope. Although the original EVL procedure was associated with fewer post-procedure bleeds than ES, the procedure was cumbersome. Furthermore, overtube passage itself carried a risk of esophageal laceration and perforation. Multiband ligating devices became available commercially in 1996. Because it became possible to load 6 or more bands onto the ligating chamber, only one passage of the endoscope was needed. Thus, the multiband ligator obviated the need for passing an overtube prior to starting EVL. Recent trials have shown that this development has increased the safety of the procedure and has increased its ease of application (59).

The first randomized trial comparing EVL with ES was reported in 1992 (60). In 1995, a total of 7 randomized trials underwent meta-analysis (50). Compared to ES, EVL significantly reduced the rebleeding rate (odds ratio = 0.52, 95% confidence interval = 0.37–0.74), the mortality rate (odds ratio = 0.67, 95% confidence interval = 0.46–0.98), and the death rate due to bleeding (odds ratio = 0.49, 95% confidence interval = 0.24–0.996). On average, it took 4 EVL sessions to obliterate varices, in contrast to 6 ES sessions. Furthermore, there were fewer treatment induced ulcers and fewer complications associated with EVL. Whereas 3.3% of ES procedures were accompanied by fatal complications, 1.0% of EVL procedures had fatal complications.

It now appears that EVL is the endoscopic procedure of choice for treating bleeding esophageal varices. However, the performance of EVL may be technically difficult in an esophagus awash in blood. ES is appropriate in this setting. At follow-up endoscopy sessions, it becomes increasingly difficult to ligate residual, partially-treated varices. A combination of EVL for large varices and ES for small varices may be warranted.

For decades, investigators have been intrigued by the challenge of preventing variceal hemorrhage in cirrhotic patients with asymptomatic varices, whether it be by surgical or endoscopic means. Although a few trials have supported the performance of prophylactic ES, the data remain inconclusive (61). The relative safety of EVL is leading endoscopists to reinvestigate the question of prophylactic endoscopic treatment. One recent abstract addressed the issue by randomizing 80 patients with varices to prophylactic EVL and 76 patients with varices to no treatment. Over a median follow-up period of 32 months, variceal bleeding occurred in 8.7% of treated patients and 36.8% of control patients ($p < 0.05$). Furthermore, the treated patients experienced a survival advantage as well, with 18.7% of the treated patients and 40.7% of the untreated patients dying during the study ($p < 0.05$). This abstract raises the possibility that prophylactic EVL may be incorporated into the management of patients with asymptomatic varices (62).

A number of alternative endoscopic approaches are being explored in treating variceal bleeding. They offer the hope that endoscopy may be refined so that bleeding gastric varices may be treated endoscopically. One approach uses sclerotherapy technique to inject the tissue adhesive N-butyl-2-cyanoacrylate in an attempt to occlude the lumen of bleeding varices. Studies employing cyanoacrylate injection for treatment of large varices, with simultaneous traditional sclerotherapy for treatment of small varices, have been associated with rebleeding rates of 10% or less. However, the technique is somewhat cumbersome and it has not yet been approved by the Food and Drug Administration for use in the United States (63).

Other techniques use the endoscope to deploy detachable clips (64) and detachable snares (65) in an effort to entrap esophageal varices and induce thrombosis. A recent report describes the successful obliteration of gastric varices in 10 patients by use of a detachable endoscopic snare (66). These devices are deserving of additional investigation.

Medical and Endoscopic Management of the Patient with Acute Variceal Bleeding

The keystone of therapy for variceal bleeding remains aggressive resuscitation with blood products. Since the early 1980s, many gastroenterologists have recommended that emergent endoscopy be performed at the earliest possible moment in order to confirm the clinical suspicion of variceal bleeding and to rule out other causes of upper gastrointestinal bleeding. Indeed, up to 50% of gastrointestinal bleeds in patients with cirrhosis are said to arise from sources other than varices. Emergent endoscopy also offers an opportunity to perform ES or EVL if varices are at the bleeding site, or cautery or epinephrine injections if there is bleeding from another site. Thus, emergent performance of endoscopy remains a tenet of the management of upper gastrointestinal bleeding.

The medical therapy of acute variceal bleeding remains controversial. In the past, concern over the potential side effects of vasopressin led many gastroenterologists to hold the use of this drug in reserve, unless the patient was experiencing massive variceal bleeding or unless bleeding was incompletely controlled by ES. In contrast, the safety profiles of somatostatin and octreotide permit clinicians to institute drug therapy in the emergency room, as soon as the diagnosis of variceal bleeding is suspected. I do not recommend either somatostatin or octreotide as monotherapy for acute variceal bleeding. In practice, I administer octreotide intravenously at 50 μg/hr for up to 5 days following a moderate or massive hemorrhage, even if there is initial endoscopic control of bleeding. This approach is supported by a recent study in which cirrhotic patients with upper gastrointestinal bleeding were randomized to intravenous somatostatin or placebo prior to undergoing emergency therapeutic endoscopy. Patients receiving both somatostatin and ES for bleeding esophageal varices required transfusion with fewer blood products than patients treated with placebo prior to ES. Furthermore, patients receiving combination therapy had a reduced requirement for rescue therapy with repeat ES, balloon tamponade or TIPS (67).

Ongoing treatment with octreotide is warranted if bleeding is incompletely controlled by initial therapeutic endoscopy. I tend towards repeating ES or EVL if there is incomplete control of bleeding or in the event of rebleeding. Treatment with a non-selective β-blocker is initiated once bleeding is well controlled and octreotide is withdrawn. In general, treatment is started with nadolol 40 mg once daily. Attempts are made to increase the dose until there is a 25% reduction in heart rate from baseline. Co-treatment with isosorbide-5-mononitrate may be offered as well.

The proper timing of follow-up endoscopy after control of initial variceal hemorrhage remains controversial. In the past, follow-up sclerotherapy was often performed 48–72 hours after initial ES. It is now recognized that re-treatment of varices at this stage may increase the risk for complications (68). Many institutions, including our own, perform follow-up therapeutic endoscopy every 1–2 weeks after the initial procedure in an effort to obliterate varices. Once varices are obliterated, patients are re-endoscoped after 3 months, and then every 6 months to assure that varices do not recur. Recurrent varices may be re-treated using either EVL or ES.

Many studies have demonstrated that a combination of β-blockers and ES is more successful at preventing variceal rebleeding than either β-blockers alone or ES alone (7). These conclusions can presumably be extended to β-blockers used in combination with EVL for secondary prophylaxis of variceal bleeding. In our practice, patients remain under treatment with β-blockers at least until the time that varices have been obliterated. The utility of β-blocker and nitrate therapy after successful obliteration of varices remains unknown.

Management of the Patient with Refractory Variceal Bleeding

About 10% of patients who suffer from esophageal variceal bleeding experience massive, continuous or recurrent bleeding which is refractory to optimal medical and endoscopic management. In practice, I attempt to perform repeat ES or EVL before declaring that a recurrent bleeding event is refractory. Other reasons for declaring that a variceal bleed is refractory include: bleeding from gastric varices (although some gastric varices may be amenable to endoscopic therapy); and two or more recurrent bleeds over the course of weeks to months in spite of aggressive endoscopic and β-blocker treatment. Patients with refractory variceal hemorrhage often require urgent or emergent decompression of the portal venous system (Fig. 1).

Patients who suffer from massive or continuous bleeding are particularly challenging to manage. Many such patients require balloon tamponade in order to stabilize them prior to performing lifesaving shunt surgery or TIPS. The Sengstaken-Blakemore tube (Davol Inc., Cranston, RI) was first introduced in 1950 (69). This device and its subsequent variations, the Minnesota tube and Linton-Nachlas tube, are passed per nares or per os in an intubated patient. Correct positioning of the tube is documented by chest and abdominal X-ray. The gastric balloon is then inflated with about 300 cc air, and gentle traction, usually about 0.5 kg using a pulley system, is applied. Sengstaken-Blakemore and Minnesota tubes are also equipped with an esophageal balloon which can permit balloon tamponade directly to bleeding esophageal varices. However, gastric balloon insufflation and traction alone is often sufficient for short-term control of either gastric or esophageal variceal bleeding. Balloon tamponade induces initial hemostasis in 40–90% cases of bleeding esophageal varices (7). However, fatal complications arise in 6–20% of cases (7). They include: necrosis of the gastroesophageal wall, rupture of the esophagus, and aspiration pneumonia. In spite of these problems, balloon tamponade should be employed as a temporizing measure

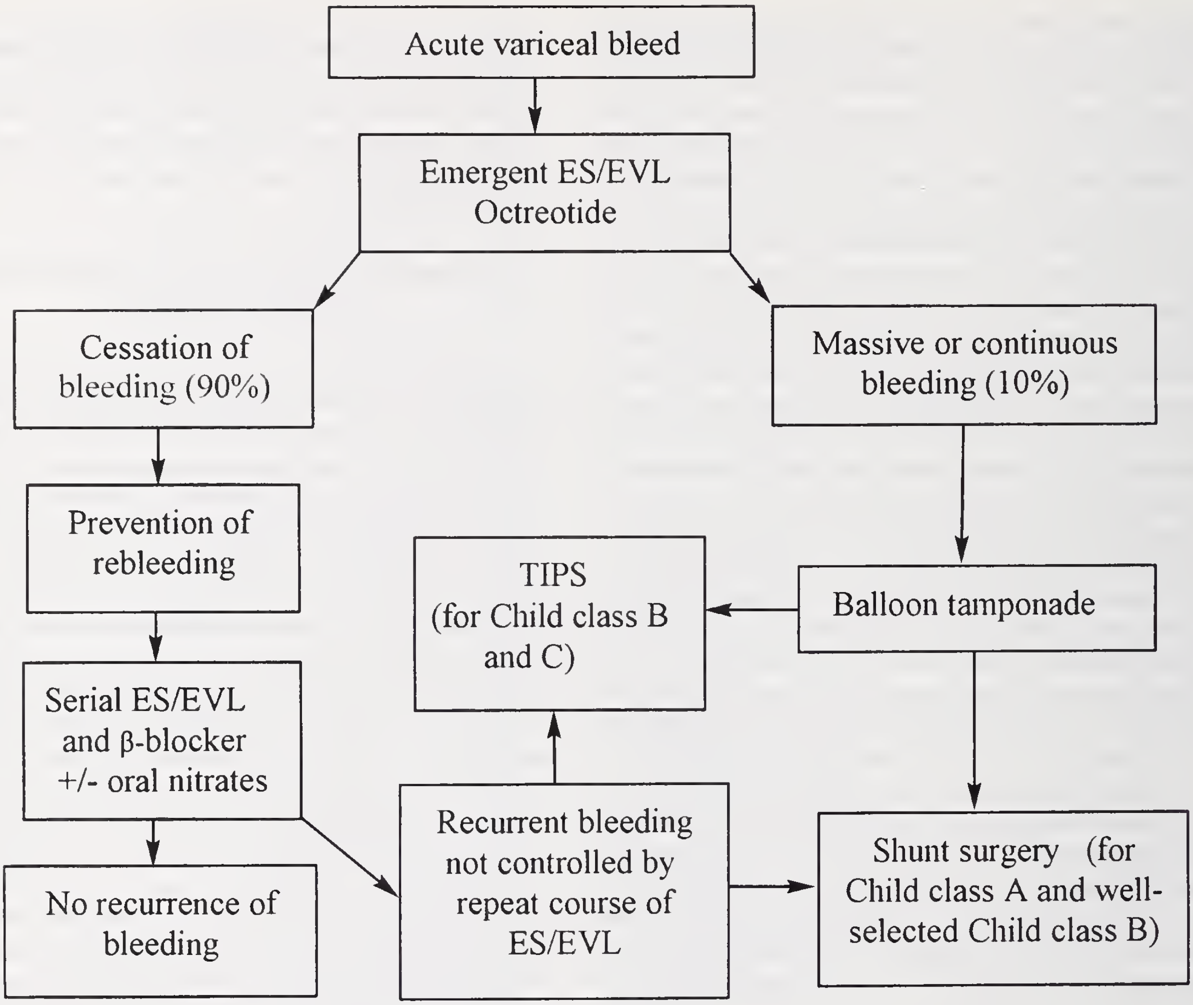
Acute variceal bleed
Emergent ES/EVL Octreotide
Cessation of bleeding (90%)
Massive or continuous bleeding (10%)
Prevention of rebleeding
TIPS (for Child class B and C)
Balloon tamponade
Serial ES/EVL and β-blocker +/- oral nitrates
Recurrent bleeding not controlled by repeat course of ES/EVL
Shunt surgery (for Child class A and well-selected Child class B)
No recurrence of bleeding

Fig. 1. Suggested Management of Acute Variceal Bleeding.

when patients with massive hemorrhage fail emergent endoscopic and medical therapies.

Portocaval shunts provide rapid, effective portal decompression and are highly successful at halting variceal bleeding. Concerns over procedural mortality and postoperative complications limit their utility in the primary treatment of acute variceal bleeding. However, 50 years after its introduction, shunt surgery, as well as its modern counterpart, TIPS, remain the mainstays of therapy for refractory variceal bleeding (Table 2).

Whipple (70), Blakemore (71), and others at Presbyterian Hospital in New York were instrumental in the development of the end-to-side portocaval shunt in 1945. It was recognized early on that many patients developed post-operative liver failure or hepatic encephalopathy. This was presumably due to the diversion of blood and nutritional substrates from patients' already compromised livers. In response to this observation, side-to-side portocaval shunt surgery was introduced a few years later. The mesocaval shunt, developed during the 1950s and 1960s, represented a variation on a theme, by interposing a Dacron graft between a large mesenteric vein and the inferior vena cava. These newer procedures

TABLE 2

History of the management of acute variceal bleeding

1950	1980	1997
Fluid resuscitation	Fluid resuscitation Endoscopy • Sclerotherapy IV medications • Vasopressin	Fluid resuscitation Endoscopy • Sclerotherapy • Variceal ligation (EVL) IV medications • Vasopressin, terlipressin • Somatostatin, octreotide
Balloon tamponade	Balloon tamponade	Balloon tamponade TIPS
Portocaval shunt	Portocaval shunt	Portocaval shunt Liver transplantation

decreased the incidence of post-operative liver failure and hepatic encephalopathy by partially maintaining blood flow to the liver.

Portocaval shunt surgery is highly effective in the initial treatment of bleeding. Only 9–22% of patients experience late episodes of rebleeding (7). This figure should be appreciated in the context of a 23–55% rebleeding rate for patients treated with sclerotherapy (72). Non-emergent portocaval shunt surgery carries with it a 7–13% operative mortality rate (73). However, operative mortality jumps to more than 50% when portocaval shunt surgery is performed emergently, especially in the patient with Child class C status (72). The most optimistic and controversial results are reported by Orloff et al. (74). They studied 43 patients who underwent surgery following variceal bleeding. Emergency portocaval shunt surgery was performed in 21 patients within 8 hours of presentation with variceal bleeding. Elective portocaval shunt surgery was performed in 22 patients who were initially stabilized by use of vasopressin and esophageal balloon tamponade. Of the patients who underwent emergent surgery, all 10 patients with Child class A or B status survived their initial hospitalization, with a 90% one-year survival rate. Seven of 11 patients with Child class C status (64%) survived initial hospitalization. Only one of these survivors died during the first year of follow-up. Survival data were significantly better for patients who underwent emergent shunt surgery than for patients who underwent elective surgery (74). Other investigators have not been able to duplicate these results (75).

Distal splenorenal shunt surgery (76) attempts to selectively decompress gastroesophageal varices by diverting splenic venous outflow into the renal vein. Splanchnic venous return to the liver is maintained. Its theoretic advantage over portocaval shunts is a decreased incidence of post-operative hepatic encephalopathy and liver failure. The surgery requires considerable technical expertise and is not appropriate in either obese patients or in the emergent setting. However, when performed in an appropriately selected patient, it is highly effective. On average, 17% of patients will suffer rebleeding, with as low as a 3% rebleeding rate described by Henderson et al. (77). There is a 9–13% operative mortality rate (73, 77).

Shunt surgery should be considered when emergent portal decompression is required in a relatively well-compensated cirrhotic patient (patients with Child class A status and well-selected patients with Child class B status). The choice of shunt operation depends upon the clinical setting and the expertise of the operator. The advent of TIPS provides us with an additional option in patients with advanced Child class B and C cirrhosis.

Work by Rosch (78), Colapinto (79), Palmaz (80) and colleagues in the 1970s and 1980s laid the groundwork for the first successful creation of TIPS in humans in 1989 (81). TIPS is physiologically equivalent to a side-to-side portocaval shunt. However, it represents a dramatic departure from portocaval shunt surgery. The procedure can be performed in the interventional radiology suite in 1–2 hours, often without the need for general anesthesia. TIPS are created by introducing a catheter into the right hepatic vein, typically using an approach through the right jugular vein. A needle is deployed within the catheter. It is briskly inserted into the liver parenchyma until it is positioned in the right portal vein. A guide wire is inserted into the portal vein, the needle is removed, and a tract through the hepatic parenchyma is created by balloon dilation. An expandable metal stent is introduced into the newly created tract between the hepatic and portal veins. The stent is balloon dilated, forming a conduit which shunts blood from the hypertensive portal vein into the hepatic vein. The result is a rapid and sustained decrease in portal pressure. Refractory variceal bleeding is particularly amenable to therapy with TIPS (82, 83). The procedure has also been used electively in order to reduce portal pressures in patients suffering from massive ascites (84, 85). However, this indication is not universally accepted (82).

TIPS procedures fail to create a shunt in up to 10% of cases. In an effort to improve the efficacy and safety of the procedure, an alternative transmesenteric-transfemoral method (tmTIPS) is used at Westchester Medical Center. With the patient under general anesthesia, a stone retrieval basket is introduced via a femoral vein approach, and positioned and opened in the hepatic vein. A mini-laparotomy is performed and a blunt directional cannula is introduced via a mesenteric approach into the selected branch of the portal vein. Under fluoroscopic guidance, a 20 gauge needle is inserted through the cannula. The hepatic parenchymal puncture is performed, the needle is grasped by the retrieval basket in the hepatic vein, and a guide wire is introduced. Control of both the mesenteric and femoral ends of the guide wire facilitates deployment of the intrahepatic stent (86). Although the transmesenteric-transfemoral technique necessitates general anesthesia and mini-laparotomy, operative complications have been minimal and there have been no direct procedure-related deaths in more than 130 cases (G. Rozenblit, personal communication). The tmTIPS procedure decreases the risk of extracapsular puncture during needle insertion through hepatic parenchyma, reduces fluoroscopy time, facilitates careful positioning of the intrahepatic stent, and is associated with a 100% technical success rate, even in the setting of portal vein thrombosis (86).

Intimal hyperplasia within the hepatic vein, pseudointimal hyperplasia within the TIPS stent, thrombosis, and stent "shortening" will cause one half of TIPS to stenose or even occlude within 1–2 years of initial placement (87, 88). Portal hypertension redevelops in these cases, placing patients at risk for recurrent variceal bleeding or the redevelopment of ascites. Most cases of severe stenosis or occlusion can be detected if patients are enrolled in a program of surveillance Doppler ultrasonography, usually scheduled every 3 months after TIPS placement. Some authors recommend routine venography to follow TIPS patency. In the vast majority of cases of TIPS stenosis, repeat angiographic intervention can successfully reestablish patency. However, at the present time, TIPS cannot be considered to be a long-term solution for the treatment of portal hypertension.

Although TIPS has not been compared to portocaval shunt surgery in a clinical trial, its procedural complication rate of about 10%, mortality rate of 1–2%, the new onset or worsening of hepatic encephalopathy in 10–30% of patients (82), and a long-term rebleeding rate of 13–22% (88–90) compare favorably with portocaval shunts. However, the low risk of surgical shunt failure and the well-known propensity of TIPS stents to stenose or occlude lead me to favor portocaval shunt surgery in the well compensated cirrhotic patient with refractory bleeding. Distal splenorenal shunt surgery is the operation of choice in patients with Child class A status. Side-to-side portocaval or mesocaval shunt surgery may be performed instead in the emergent setting or if technical factors are likely to interfere with the creation of a distal splenorenal shunt. However, a majority of patients with refractory variceal bleeding have Child class B and C status. TIPS is the treatment of choice for these patients, recognizing that patients will require life-long ultrasonographic and angiographic surveillance.

It remains unclear if TIPS should be employed after a patient's initial variceal bleed in an effort to reduce the risk of rebleeding and improve long-term survival. As an example, two simultaneously published studies reached different conclusions after randomizing patients to receive either multiple sclerotherapy sessions or TIPS, following control of patients' index variceal hemorrhages by ES. Cello et al. (89) reported that 13% of patients undergoing TIPS and 48% of patients undergoing ES rebled from varices ($p = 0.012$). A trend toward improved survival was noted in the TIPS group. Sanyal et al. (90) reported that 22% of patients undergoing TIPS and 21% of patients undergoing ES rebled from varices ($p = NS$). Also, patients in the TIPS group had a higher mortality rate than patients in the sclerotherapy group. In my opinion, it remains premature to recommend TIPS for patients who have not received an adequate trial of ES or EVL, with or without co-therapy with β-blockers and nitrates.

A number of other surgical interventions have been performed in patients with acute variceal bleeding. Esophageal transection and reanastomosis by an EEA stapler, occasionally combined with devascularization of the proximal stomach, is frequently employed in the United Kingdom and Japan (91–94). Liver transplantation has also been used successfully to salvage patients with active, uncontrollable variceal bleeding (95). However, patient instability prior to liver transplantation increases the chance for intra-operative bleeding and post-operative infection, thus jeopardizing the overall success of transplant. Given the critical shortage of donor organs, emergent transplant should only be offered to patients if: a) there is no suspicion for underlying infection, and b) variceal bleeding continues in spite of attempts at TIPS or shunt surgery. Because a history of variceal bleeding increases a patient's chance of early morbidity and mortality, it should be factored into any decision with respect to timing of liver transplantation.

What Is the Future?

The use of multi-band ligating devices will grow in popularity over the next few years. The devices' technical ease of operation, and their favorable complication rate, make EVL the endoscopic treatment of choice in the patient with acute variceal bleeding. However, gastroenterologists will still need to be well versed in the performance of ES, as small esophageal varices might not be amenable to treatment with EVL. Widespread availability of EVL will result in the more aggressive use of this modality as secondary prophylaxis against variceal bleeding. We can also anticipate a resurgence of clinical interest in exploring EVL as primary prophylaxis against variceal bleeding. Although previous primary prophylaxis trials studying portocaval shunt surgery and ES did not conclusively demonstrate a survival advantage for patients treated with either modality, the low side effect profile of EVL may tip the balance in favor of prophylactic therapy in well-specified subsets of patients. Individuals with well-compensated liver disease and large varices would appear to be particularly appropriate subjects to study. Additional clinical experience with detachable endoscopic clips and snares and with injectable tissue adhesives may make their use popular in the endoscopic therapy of gastric varices. This may save some patients with gastric varices from otherwise obligatory portal decompression.

Primary and secondary prophylactic therapies with β-blockers and nitrates are likely to gain increasing acceptance over the next few years. We hope to see trials that explore novel drugs which target specific mediators of splanchnic vasodilation.

Work is ongoing to improve the long term patency of TIPS shunts by using covered stents (96). Other groups are attempting to determine the optimal diameter of the TIPS stent at time of initial deployment so that the risk of post-TIPS hepatic encephalopathy and liver dysfunction can be reduced.

Finally, clinicians look forward to the day that we can unlock the secrets of hepatic fibrogenesis. Medical therapy might then be able to forestall the development of hepatic fibrosis and cirrhosis in patients with liver disease. With such an advance, we might then substantially reduce the incidence of life-threatening complications of portal hypertension.

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Past, Present and Future of End-Stage Renal Disease Therapy in the United States

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Abstract

Dialysis was first described and used in 1854 to separate substances in aqueous solution based on different rates of diffusion through a semipermeable membrane. *In vivo* hemodialysis was performed in animals early in the twentieth century. Hemodialysis was first carried out in patients with acute renal failure in The Netherlands during the Second World War and in the United States in 1948. Repetitive hemodialysis for the treatment of chronic renal failure due to end-stage renal disease had to await the development of an acceptable long-lasting vascular access in 1960. The subsequent successful development of a technique to create an adequate arteriovenous fistula in 1972 permitted the rapid growth of dialysis programs, when the cost of this therapy was largely paid for by Medicare. Equipment has been developed to foster home-care hemodialysis and chronic ambulatory peritoneal dialysis.

Enhancements in renal replacement therapy included the availability of recombinant human erythropoietin, calcitriol, and effective antihypertensive drugs. Technical advances in hemodialysis followed the use of bicarbonate dialysate, more biocompatible membranes, membranes of higher porosity, and ultrafiltration. Questions remain regarding the evaluation of the adequacy of dialysis which is to be achieved or prescribed.

Careful attention to the management of the patient with progressive chronic renal insufficiency is crucial in dealing with the inevitable onset of uremia and the initiation of dialysis and/or renal transplantation. The cost of renal replacement therefore represents a great societal burden. A better understanding of how to prevent onset and progression of specific nephropathies along with the availability of new and more effective equipment for renal replacement therapy has a high priority. *- Editor*

Key Words: End-stage renal disease, dialysis techniques, progression of renal disease, vascular access, Kt/V.

Introduction

The essence of this presentation can be summarized as follows: Before 1960, end-stage renal disease (ESRD) meant unavoidable death; in 1997, there were about 250,000 patients with ESRD being kept alive in this country with a variety of renal replacement therapies. The dramatic change which took place over the course of four decades represents a story of fantastic medical success which I will now review.

Historical Perspective

The term "dialysis" was coined in 1854 by the Scottish chemist Thomas Graham to refer to the separation of substances from solution based on their different diffusion through a semipermeable membrane. Graham performed a variety of *in vitro* experiments of the movements of various solutes through dialysis membranes (1). The English scientist D.W. Richardson made the first *in vitro* dialysis of human blood in 1889. He coined the term "crystalloid" to refer to solutes of the blood which readily passed through the membrane and "colloid" for those which did not (1). Abel, Rowntree and Turner, working at Johns Hopkins University, performed the first *in vivo* dialysis, but only in animals (1). Hass in Germany is credited with performing the first dialysis in humans (1). In 1944, Kolff and Berk designed the rotating-drum artificial kidney, the first truly functional hemodialysis apparatus (2). At the end of the Second World War, Kolff sent some of his artificial kidneys as a gift to several countries; one of these kidneys came to The Mount Sinai Hospital, where in 1948 it was first utilized to perform hemodialysis in a patient with bichloride of mercury poisoning (3).

While the technical capacity to perform dialysis was already available to treat patients with

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acute renal failure before 1960, the lack of an acceptable long-term vascular access limited the use of dialysis for the prolonged treatment of chronic renal failure. Frequent cannulation of peripheral veins led to inadequate flow, inflammation, thrombosis and eventual loss of these veins. In reality, after a few months, the patient would no longer have any accessible veins with which to continue dialysis. Thus, the single most important contribution to the establishment of chronic hemodialysis was the creation of the Quinton-Scribner shunt in 1960 (4). Unfortunately, this external arteriovenous shunt was plagued by infection and thrombosis. A major advance in the vascular access problem took place in 1966 with the creation of an arteriovenous fistula in the forearm by Brescia et al. (5). The endogenous arteriovenous fistula immediately became, and still remains, the gold standard of vascular access for chronic hemodialysis.

The advent of the Brescia-Cimino arteriovenous fistula initiated the era of chronic hemodialysis, but the new technique was expensive and only a limited number of patients could be admitted to the few chronic dialysis programs then established throughout the country. In 1972, the federal government expanded Medicare to include payment of 80% of the cost of renal replacement therapy (6). The growth of ESRD therapy in this country thereafter was dramatic. At the present time, approximately a quarter of a million people are being maintained with renal replacement therapy.

Recent Advances in the Treatment of ESRD

There have been 3 main recent advances which have had a great influence in the treatment of patients with chronic renal insufficiency:

- Availability of recombinant human erythropoietin, which has allowed the virtual elimination of severe anemia in ESRD patients. Data from the United States Renal Data System (USRDS) show that the average hematocrit of dialysis patients in the United States has increased from 27% in 1989, the year when erythropoietin was introduced, to about 32% in 1995 (7). Medicare recently approved an increment in the allowable level of hematocrit, which most likely will produce further increases in the value on a national basis.
- Availability of calcitriol [1,25$(OH)_2$-vitamin D], the active form of vitamin D, which together with dietary phosphate restrictions and the use of intestinal phosphate binders should minimize the consequences of renal osteodystrophy and severe secondary hyperparathyroidism in patients with ESRD (8).
- A large armamentarium of medications to control blood pressure in most patients with chronic renal insufficiency.

The availability of exogenous erythropoietin and calcitriol permits pharmacological replacement of most of these endocrine functions of the kidney. However, we still cannot replace the excretory function of the kidney, except through dialysis or transplantation. Sufficient amounts of sodium and water can be eliminated via the gastrointestinal tract, particularly if a poorly absorbed sugar such as sorbitol is administered to induce enough diarrhea. The oral administration of cation-exchange polystyrene (Kayexalate®) resins can enhance the fecal loss of potassium and thereby offset the daily dietary intake of potassium. The obvious disadvantage of this approach is the diarrhea, but many patients would be ready to accept 1 – 3 loose bowel movements per day rather than dialysis. Unfortunately, none of these possible maneuvers correct the uremic syndrome and prolong survival (9, 10).

Main Advances in Dialytic Therapy

The main technical advances in hemodialysis have been (11, 12):

- Introduction of bicarbonate dialysate which allows the elimination of acetate as the alkali source with a significant improvement of symptoms during dialysis.
- Development of more biocompatible membranes for dialyzers. Biocompatibilty is defined in terms of the extent to which membranes activate the complement cascade after being exposed to blood. A completely biocompatible membrane does not activate complement.
- Introduction of membranes of higher porosity which may be able to increase the removal of middle molecules.
- Development of dialysis machines with the capability of programming the concentrations of sodium and bicarbonate in the dialysate.
- Development of dialysis machines which can be scheduled to ensure accurate removal of fluid by ultrafiltration during the treatment.
- High-efficiency hemodialysis allowing for less real time on dialysis without sacrificing the amount of small molecular solutes removed.
- A somewhat better understanding of what adequacy of dialysis means through more

widespread use of the concept of Kt/V, a numerical index of dialysis adequacy. Kt/V is a dimensionless parameter which is calculated from the dialyzer urea clearance (K), duration of dialysis (t) and volume of distribution of urea in the body (V).

At present, a typical hemodialysis prescription includes 3 treatments per week of 3–4 hours, each with a reusable dialyzer of surface area of more than 1 M^2. An extracorporeal blood flow rate of 300–500 ml/min is targeted, while the dialysate flow rate is maintained at 500–800 ml/min. The aim of each hemodialysis session is to achieve a Kt/V in excess of 1.2/session.

The main advances in peritoneal dialysis have been (13, 14):

- The establishment and development of chronic peritoneal dialysis as an alternative modality of renal treatment for ESRD patients during the past 3 decades.
- Development in the techniques of connecting peritoneal catheters to dialysate bags, which significantly diminish the incidence of peritonitis to a current average of about one episode of peritonitis/patient/1.5 years.
- Development of new, compact, almost noiseless programmable machines capable of automatically cycling peritoneal dialysis fluid in and out at night while the patient sleeps.
- A somewhat better understanding of what adequacy of dialysis means through the general use of the Kt/V, already defined above.

There are 2 main forms of chronic peritoneal dialysis: Continuous Ambulatory Peritoneal Dialysis (CAPD) and Automatic Peritoneal Dialysis (APD). The typical prescription in CAPD is 4–5 exchanges per day of 2–3 liters each. For APD, most of the exchanges take place at night with a dwell time that may vary from one to several hours. Many patients may need to add a manual exchange during the daytime.

Approach to the Patient in the Pre-ESRD Phase

The most important parameters of medical care for patients with chronic renal insufficiency include:

- Attempts at slowing down the progression to ESRD with maneuvers such as dietary protein restriction, tight blood pressure control and the use of ACE inhibitors.
- Normalization of the blood pressure.
- Normalization of serum calcium and serum phosphorus.
- Normalization of hematocrit.
- Avoidance of nephrotoxic drugs.
- Treatment of urinary tract infection.

The patient with chronic renal disease who is experiencing progressive loss of renal function should be aware of, and not surprised about, the possible need for dialysis or transplantation. Formulating a life plan is an important element in the strategy to deal with the inevitable onset of uremia (15). This planning includes the projection of a probable course to ESRD, assessment of possible renal transplantation and the choice of dialysis modality. Once the patient and physician decide on hemodialysis, planning for early creation of vascular access is essential.

Determining when to initiate dialysis in the course of the progressive worsening in renal function is controversial (16). No single factor provides guidelines for every patient. For example, an asymptomatic 40-year-old man with a serum creatinine of 10 mg/dl as the result of slow progression of polycystic kidney disease may still get by on conservative therapy, while a 40-year-old woman with a serum creatinine of 5 mg/dl secondary to progression of diabetic nephropathy and concomitant congestive heart failure may benefit from initiation of dialysis. One extreme is the work of Bonomini et al. (17) in Bologna, who advocate initiation of dialysis at residual creatinine clearances between 15–20 ml/min. These authors have reported much better survival rates in patients who are started early on dialysis.

Modality of Therapy Choice

The ideal therapy for ESRD should be the implantation of an immunologically inert allogeneic or xenogeneic kidney graft or the implantation of an artificial organ capable of replacing deficient excretory function. Obviously, we are not at this stage yet, and because of the scarcity of organs available for kidney transplantation, most patients reaching ESRD will have to choose a modality of dialysis therapy.

No prospective, controlled, randomized studies have examined the effect of modality of therapy on morbidity and mortality. The prevalent sensitivity to patient preference and to patient rights precludes such a trial. As a result, lacking experimental data, the physician must rely on uncontrolled trials, personal experience and intuition ("clinical judgment") to determine the best modality of dialysis (15).

Tables 1 and 2 summarize the advantages and disadvantages of both peritoneal dialysis and hemodialysis. All of the enumerated disadvantages of in-center hemodialysis can be eliminated with daily nocturnal home hemodialysis (DNHH) (18): (a) daily removal of fluid eliminates the need for wide swings in the volume and body chemistry status; (b) a lower rate of blood flow allows the utilization of a transcutaneous double lumen catheter for vascular access if a fistula is not available; and (c) one can initiate treatment with about 2 hours of daily treatment at a blood flow rate of about 200 ml/min.

Unfortunately, DNHH requires the availability of a dialysis machine which is capable of both automatically cleaning and testing the dialyzer for reuse as well as regenerating dialysate fluid locally. The second important requirement for this modality of therapy is the presence of a second person at home to assist with the vascular access and possible troubleshooting during treatment. However, once these dialysis machines become commercially available, DNHH may become an important alternative modality of dialysis therapy.

How to Evaluate Adequacy of Dialysis

The National Cooperative Dialysis Study (NCDS) in the 1980s was the first to establish some guidelines for hemodialysis prescriptions. This study randomized 160 patients into four treatment options: low vs high BUN and short vs long treatment time (19). The study showed that patients with higher BUN had greater morbidity and mortality than those with lower BUN concentrations. Later analysis of the data by Gotch and Sargent (20) emphasized the concept of Kt/V as an index of dialysis adequacy. For the nonnephrologist, it should suffice to know that Kt/V is a value directly calculated from the BUN values obtained pre- and post-dialysis. The greater the numerical value of Kt/V, the greater is the dose of dialysis delivered.

Several other studies have helped to confirm the notion that there is a direct relationship between dialysis dose and outcome. I will review the most representative of these studies. Owen et al. (21), in a retrospective analysis of data during a single dialysis treatment in 13,473 patients, showed that the urea reduction rate (ratio between the intradialytic decrement in BUN concentration and the pre-dialysis BUN concentration expressed as a percentage) was inversely correlated with the risk of death; a decrease in urea reduction ratio from greater than 70% to less than 45% was associated with an increased odds ratio for death from 1.04 to 1.84. Parker et al. (22) showed that an increase in the average Kt/V from 1.18 in 1989 to 1.46 in 1992 was associated with a decrease in the crude annual mortality rate from 23% to 17%. Hakim et al. (23) showed that an increase in Kt/V from 0.82 in 1988 to 1.18 in 1991 was associated with a decrease in the gross rate of mortality from 22.8% to 9.1%.

Despite all of the above information, there were no official standards for hemodialysis dosing until the NIH convened a panel of invited experts in 1993 to develop a consensus regarding the minimal dose of dialysis to be achieved. Although a safe level of Kt/V of 1.0 for each of 3 weekly hemodialyses had been recommended before, based on data derived from the NCDS, this panel now recommended an increase to 1.2 (24). Several factors played a role in changing

TABLE 1

Advantages and Disadvantages of Chronic Peritoneal Dialysis

Advantages
continuous process maintains steady-state blood chemistry values
slow removal of fluid is gentle on the cardiovascular system
almost perfect control of blood pressure
more freedom in food and fluid intake
patients have full control on the treatment
survival seems to be comparable to hemodialysis

Disadvantages
low clearance forces for continuous or semicontinuous treatment and limits the maximal Kt/V delivered in anuric patients
significant daily glucose load
high incidence of abdominal hernias
risk of peritonitis

TABLE 2

Advantages and Disadvantages of Chronic Hemodialysis

Advantages
high clearances allow for intermittent therapy, i.e., 3 times weekly
survival seems to be comparable to peritoneal dialysis, although it is theoretically possible that higher current levels of Kt/V might produce better outcome than PD
no glucose load
no predisposition to abdominal hernias

Disadvantages
intermittent process gives unsteady chemistry values
rather fast removal of fluid is sometimes stressful to the cardiovascular system
variation in fluid status makes continuous blood pressure control almost impossible
less freedom in food and fluid intake
patients have less control on their treatment
risk of vascular access infection and thrombosis

the level of Kt/V recommended. These included the fact that patients in the NCDS had been highly selected and were in relatively good health. Patient follow-up was short. Existence of more recent data suggested that patients with comorbid conditions required more dialysis, particularly since the target value of 1.0 for Kt/V almost guaranteed that a percentage of patients would be underdialyzed. Finally, it was shown that more dialysis could be delivered safely despite variations in equipment and measurements in different dialysis units. More recently, the results of the USRDS Case Mix Adequacy Study (25), also supported the target Kt/V value of 1.2 set by the NIH Consensus.

The definition of adequacy of peritoneal dialysis has also changed over time, but the effect of varying dialysis doses on an outcome was not clearly established until the results of the CANUSA Study became available (26). The CANUSA Study, a multicenter study of CAPD patients from Canada and the United States, concluded that a weekly Kt/V in CAPD of 2.1 or a Ccr of 70L/wk/1.73M^2 is associated with a better outcome (26).

How Are We Doing?

The crude annual mortality rate of dialysis patients has remained at about 20% in the United States (7). An analysis of the causes of death shows that cardiovascular disease is responsible for approximately 50% of this mortality while infection causes about 15% (7). The usual risk factors for coronary artery disease are present and include hypertension, smoking, and hypercholesterolemia. However, there are some risk factors more specifically associated with renal disease, such as anemia, hyperphosphatemia, hyperparathyroidism and hyperhomocysteinemia (27).

An emphasis on the prevention of these risk factors should be a strong clinical consideration in the medical approach to these patients. Unfortunately, this situation is complicated by the increasing age of the population as well as numbers of patients with diabetes mellitus being dialyzed.

International Comparisons

The mortality rate for ESRD patients in the United States, about 20% per year, is higher than in most other industrialized nations (28). This fact has generated a great deal of controversy in the dialysis community. Friedman (29) has offered several reasons why American mortality rates are higher: (a) European countries ration ESRD treatment by age, sex and comorbidity; (b) European countries seem to underreport deaths; and (c) low kidney transplant rates in Japan may improve dialysis outcomes by increasing the proportion of younger and relatively healthier patients on hemodialysis. However, a number of studies have suggested that a major cause of the high mortality in the United States is underdialysis (30, 31). The recent trend toward increasing the delivered Kt/V in the United States may help physicians decide whether this increase in dialysis dose is associated with a better outcome (7). Unfortunately, the simultaneous trend toward an increase in the mean age of ESRD patients may cast some doubt on any conclusions (7).

Cost of Treatment

When the Social Security Administration assumed responsibility for payment of 80% of the costs of treating ESRD, it was anticipated that as much as half a billion healthcare dollars might be expended annually. The current yearly cost is as much as $13 billions (7). Thus, the cost of treating ESRD is beyond the budget of underdeveloped and developing nations (32).

Future Perspectives

The current decade has seen a fantastic development of techniques of molecular medicine that offer the promise of dramatic advances not only in the prevention of ESRD but also in the area of renal replacement therapy (33). This whole field is open to every kind of speculation. It may be useful to consider new and perhaps even radical proposals. I will summarize just a few of the areas where advances can make real changes.

- Advances in the area of renal transplantation: better immunosuppressive regimens for allotransplants and/or xenotransplants (34).
- Development of an implantable, fully-bionic artificial kidney (35).
- Development of dialysis machines for daily nightly home hemodialysis. This may enable a good number of patients to move from a center to home dialysis. The question of whether indigent, undereducated patients are suitable for home hemodialysis has been answered affirmatively (6).
- Design of an on-line system to create solutions for individual patients.
- Development of bioengineered bacterial flora to recycle urea and other nitrogenous compounds back into amino acids and protein in

the gastrointestinal tract (36). The assumption here is that uremia is mostly the result of nitrogenous compounds.

- Ability to genetically transfer all the required metabolic machinery to the mesothelial cells of the peritoneal cavity so that they can recycle nonprotein nitrogen into amino acids and proteins (37).
- A charged macromolecular polymer to be affixed to peritoneal mesothelial cells. This polymer will provide the osmotic force to draw water into the peritoneal space. This fluid could then be eliminated via the bladder coupled to a valved one-way pump (38).
- Rapid progress in the prevention of specific nephropathies: for example, successful implantation of pancreatic cells might reduce the number of patients progressing to ESRD from diabetic nephropathy in the coming decade (39).

It may be argued that due to advances in transplantation there will be no need for dialysis in the near future, but the overall lack of transplantable kidneys, the aging of the population and personal preference most likely will keep at least a proportion of ESRD patients on dialysis through the 21st century.

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Twelve-Year Experience with Expanded Polytetrafluoroethylene in the Repair of Abdominal Wall Defects

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Abstract

Background: A prosthetic device must be used to repair ventral hernias in patients with insufficient tissue for a tension-free primary closure. Several prosthetic materials have been employed for this purpose, with varying results. We here review a long experience with the use of expanded polytetrafluoroethylene (ePTFE) patches in the open repair of large abdominal wall defects.

Methods: Demographic, operative, follow-up, and histologic data were recorded and analyzed for all patients in a surgical practice who were treated for large abdominal wall defects with open repair using ePTFE patches between November 1983 and March 1996.

Results: Ventral hernia repairs using an ePTFE patch were performed in 98 patients. In 48 (49%), the patient had already undergone at least one previous ventral hernia repair. Of the 98 operations, 78 were full-thickness repairs, 11 were Rives-Stoppa procedures, and 9 were onlay operations. Complications included 5 seromas, 3 fistulas related to removal of a previously implanted prosthesis, and 9 infections. In addition, 10 patients developed recurrent hernias not related to explantation of the patch because of infection or fistula. In 3 patients, infections were treated successfully without removal of the patch. There were no complications related to adhesions, erosion of the patch into the viscera, or bowel obstruction. Histologic studies of long-term ePTFE implants showed excellent fibrous tissue ingrowth and minimal foreign body response.

Conclusions: Our long-term clinical experience indicates that prosthetic patches of ePTFE are safe and effective when used in the repair of large abdominal wall defects that cannot be closed primarily. Operative complications were within acceptable limits, as was the reherniation rate. **Key Words:** Hernia, ventral, incisional, polytetrafluoroethylene, herniorrhaphy.

The exact incidence of ventral or incisional hernia occurring after surgical procedures is unknown, but probably ranges between 2% and 11% (1). Therefore, repair of incisional hernias remains a common surgical procedure. Most of these hernias can be closed primarily, but use of a prosthesis is indicated in cases where there is insufficient viable tissue to permit a repair that does not place excessive tension on the suture line. Recurrence rates as high as 30% have been observed among patients in whom abdominal wall hernias were repaired without a prosthetic material (2).

Since 1983, we have used expanded polytetrafluoroethylene (ePTFE) patches (GORE-TEX® Soft Tissue Patch or, most recently, GORE-TEX® MycroMesh Biomaterial, W.L. Gore & Associates, Flagstaff, AZ) in the open repair of abdominal wall defects that could not be closed primarily. Our initial experience with these prostheses in 28 patients (3) was favorable. We have continued to employ ePTFE patches for ventral and incisional hernia repair, and here describe our entire 12-year experience with those materials.

Methods

All procedures were performed after administration of a broad-spectrum antibiotic. The fascial margins of the hernia were identified before entry into the peritoneal cavity. After entry, any loops of intestine adherent to the parietal peritoneum near the fascial margin were dissected free. Possible tension on the wound was then assessed, and if a tension-free repair could be performed, the wound was closed with interrupted sutures. If not, an ePTFE patch was implanted.

Three principal types of repairs were performed: full-thickness replacement of the abdominal wall (3), in which the prosthesis was sutured

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to the edges of the fascial defect; onlay operations, in which the fascia was closed and the prosthesis laid on top of it; and Rives-Stoppa repairs, in which the patch was placed between the rectus abdominis muscle and the posterior sheath (4). All patches were trimmed to bridge the defect. When full-thickness replacement was performed, no attempt was made to reestablish the peritoneum between the patch and the underlying viscera. The patch was tailored so that normal abdominal contours were restored, with minimal tension placed on the repair. No drains were used. Antibiotic therapy was discontinued three to five days after surgery unless there was evidence of wound infection. The surgical wound was examined daily during the patient's hospital stay, to monitor the progress of healing and to check for evidence of infection, erythema, induration, tenderness, seroma, hematoma, or abscess formation.

Demographic, operative, and follow-up data on all patients were collected retrospectively and for analysis. Specimens of an implanted ePTFE patch obtained by biopsy during subsequent abdominal procedures, performed for indications not related to the abdominal wall defect repaired with the patch, were examined histologically and with transmission electron microscopy.

Results

A total of 98 abdominal wall repairs using an ePTFE patch were performed between November 1983 and March 1996. The age of the patients ranged from 24 to 79 years (mean, 58 years); 47 were men and 51 were women. In 48 cases (49%), the patient was undergoing repair of a recurrent ventral hernia. Of the 98 operations, 78 were full-thickness repairs, 11 were Rives-Stoppa procedures, and 9 were onlay operations. The sizes of the patches used ranged from about 2×2 cm to 30×20 cm.

Postoperative complications are shown in the table. Two patients with parastomal hernias developed infections which were thought to be due to contamination. The 3 patients in whom a fistula developed all had a previously implanted prosthesis (polypropylene mesh in two patients and an ePTFE patch in one) removed during the repair. In one of these patients, a remnant of polypropylene mesh was found at the site of the fistula. Of the 9 patients with infections, 3 were successfully treated without removing the patch.

With a mean implant duration of 6.2 years (range, 56 days to 12.5 years), there were 19 reherniations (19% overall recurrence rate). However, 9 of these occurred after removal of the ePTFE patch because of infection or fistula. Recurrence occurred with the patch in place in 10 patients, all of whom had undergone at least one previous ventral hernia repair. Other than the 3 patients in whom removal of a previously implanted prosthesis led to a small bowel injury and subsequent development of a fistula, no patient had complications related to adhesions, erosion of patch material into the viscera, or bowel obstruction. Seromas developed in 5 patients.

Table

Complications after 98 Open Ventral Hernias Repairs Using an Expanded Polytetrafluoroethylene Patch

	No. of Cases
Seroma	5
Fistula	3
Infection	9
Recurrence	19
Explantation after infection or fistula	9
Explantation in patients with no infection	10*

* In patients who had undergone at least one previous ventral hernia repair.

Figs. 1–4 show portions of the ePTFE patch in one patient obtained by biopsy during two subsequent abdominal procedures performed for indications not related to the wall defect repaired with the patch. There was no recurrence of the hernia and the patch itself was not removed. Only biopsy specimens of the patch were obtained. Fig. 1 shows the histology of the specimen obtained after 7.5 years of implantation. Fig. 4 illustrates the histology of a specimen of the same patch acquired 2.5 years later, or 10 years after the original procedure. Both specimens show minimal tis-

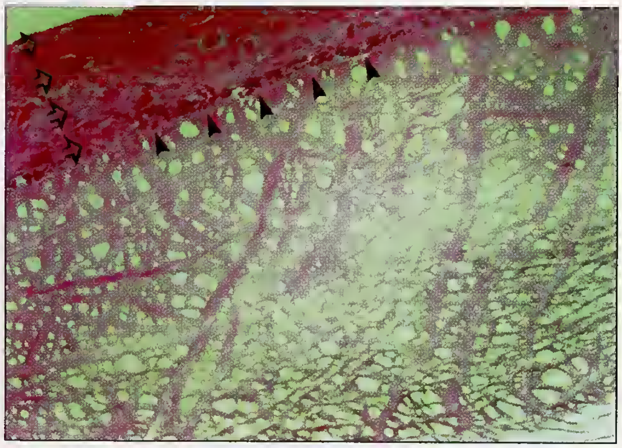

Fig. 1. Histologic study of a biopsy specimen of an ePTFE patch implanted during a ventral hernia repair 7.5 years earlier. There is a minimal cellular layer at the tissue interface (arrowheads) that consists primarily of fibroblasts, macrophages, and a rare foreign-body giant cell. The stroma is well-organized fibrovascular connective tissue (open arrows) (hematoxylin & eosin, original magnification × 25).

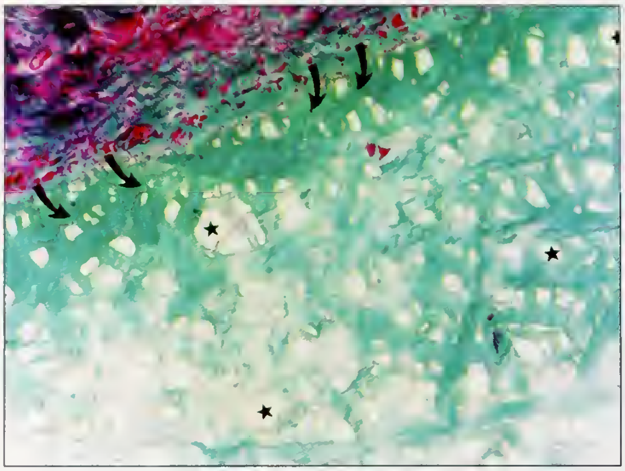

Fig. 2. Section of same specimen as in Fig. 1. Collagen formation (green) extends (curved arrows) from the periimplant stroma deep into the internodal spaces of the ePTFE, thereby creating a contiguous connective tissue matrix. The stars mark some nodes of ePTFE (Milligan's trichrome, original magnification × 25).

sue reaction to the ePTFE at the interface with the device. There are a few macrophages, some rare giant cells, and no evidence of any focal or diffuse cellular response. The extent of the host reaction appears to be less in the specimen obtained after 10 years, as compared to that obtained after 7.5 years. The connective tissue formed around the implant is nonprogressive.

In Fig. 2, the same specimen as in Fig. 1 shows extensive amounts of collagen (green stain) in the internodal spaces of the ePTFE, thereby indicating that the implant has been incorporated into the host tissue. This high degree of tissue ingrowth is consistent with a strong hernia repair. In addition, a comparison between this specimen and that shown in Fig. 4 reveals that there was a diminution in the response to foreign body during the 2.5-year interval between biopsies. In Fig. 4, fewer cells appear to be present at the interface (the site of typical cell-mediated responses to a reactive material), although the stromal component (collagen) remains inside the ePTFE pores.

Fig. 3A and 3B are ultrastructural studies of the same specimen as in Figs. 1 and 2. They con-

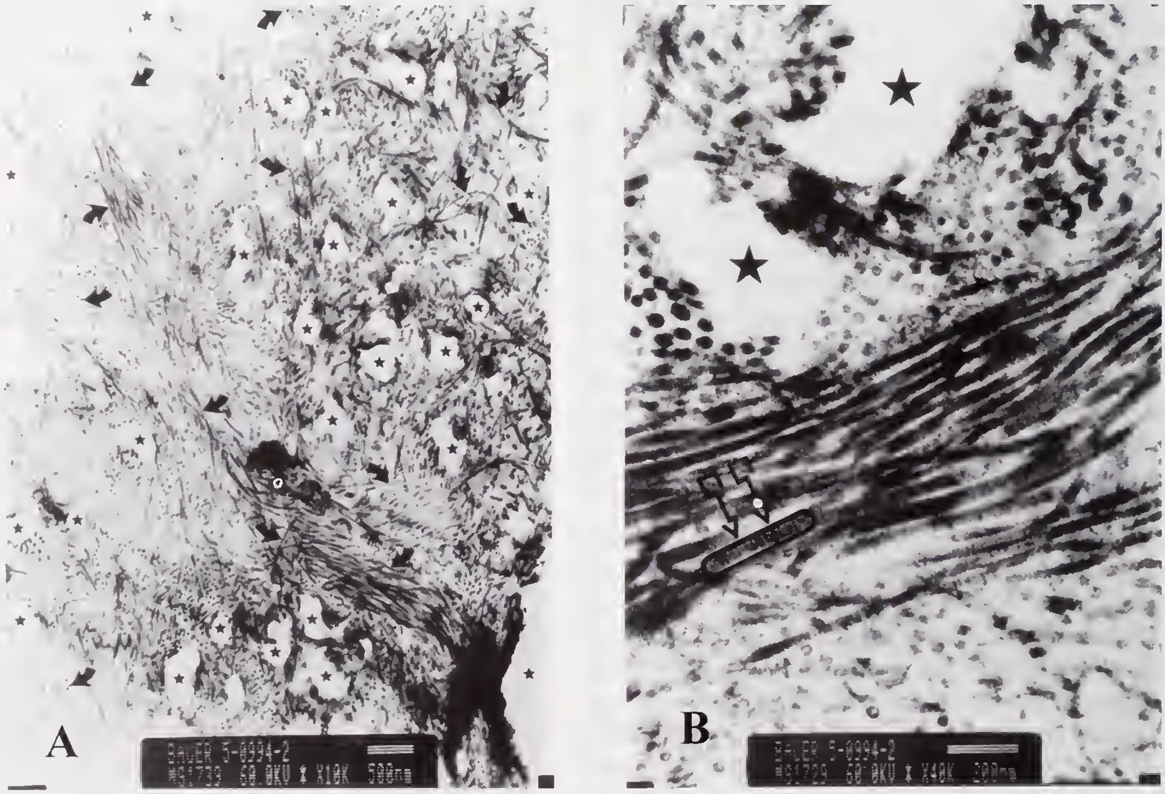

Fig. 3. Transmission electron micrographs of the same specimen as in Fig. 1. The specimen was deparaffinized and reprocessed in plastic for ultrastructural analysis. **A.** Extensive collagen fibril deposition (curved arrows) appears within the internodal spaces. Collagen, a fibrillar protein, appears in the longitudinal plane as elongated fibrils and fibril bundles and in the transverse plane as small dots or rods. The nodes of ePTFE (stars) are electron lucent and appear bright white (uranyl acetate and lead citrate, bar = 500 nm). **B.** Very high magnification shows the characteristic fibril periodicity (transverse banding along the fibril), constituting proof that these fibrils are collagen (bar = 200 nm). The periodicity is most evident in the area in which the fibrils are in the transverse plane (open arrows and oval), adjacent to two nodes of ePTFE (stars).

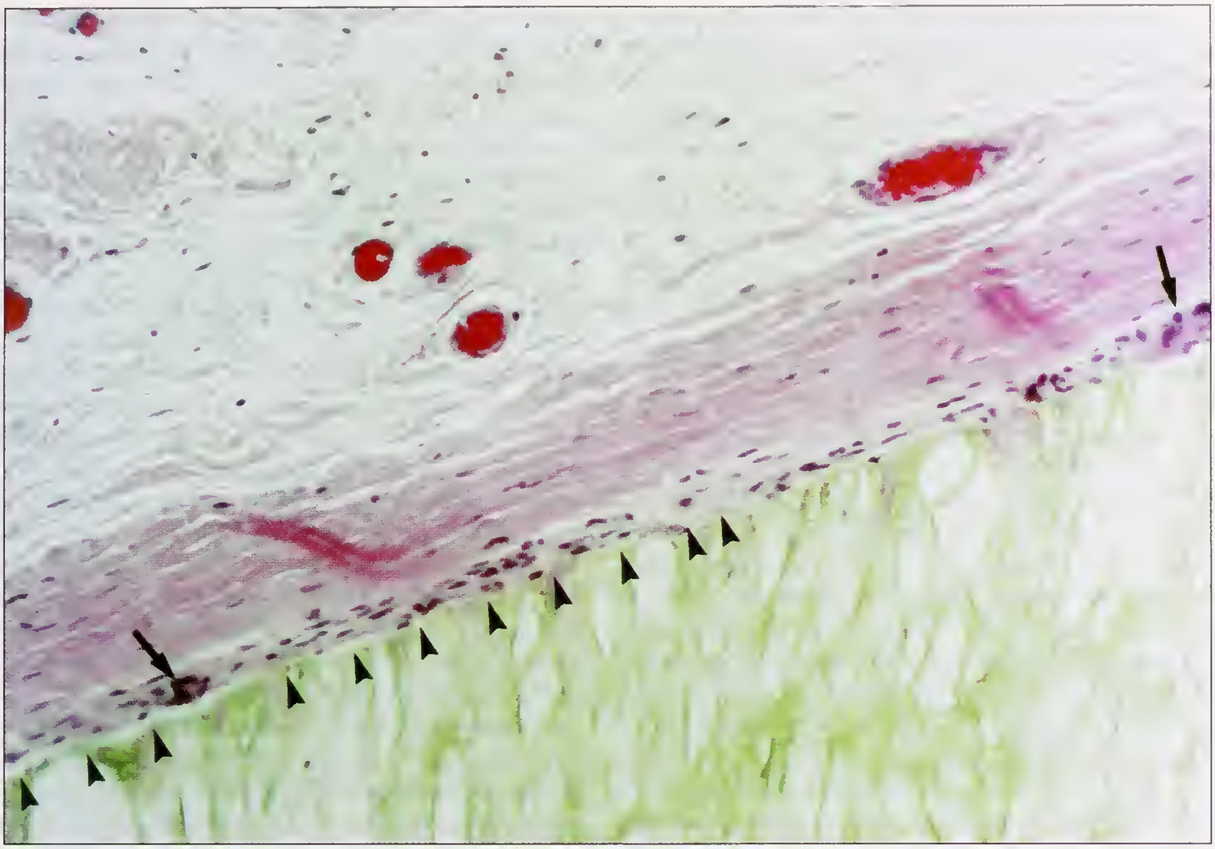

Fig. 4. Histologic study of a specimen of the same ePTFE patch as in Fig. 1 but obtained 10 years after implantation of the patch. The specimen was obtained by biopsy during a ventral hernia repair lateral to the original implantation. It is remarkable for the bland, almost nonexistent, foreign body response at the implant–tissue interface. Large areas of the interface consist only of an oriented collagenous tissue (arrowheads). Two foreign-body giant cells (arrows) are present (H & E, original magnification × 50).

firm that the trichrome staining in Fig. 2 is indeed highlighting extensive collagen fibril deposition within the ePTFE.

Discussion

In our 12-year experience with ePTFE patches in the open repair of large abdominal wall defects, we have found these prostheses to be safe and effective. Complication rates were within acceptable limits and similar to those associated with the use of any prosthetic in patients with large ventral hernias. Our current findings support those of other clinical series that have been described since our earlier report in 1987 (3).

Deysine's (5) series included 47 ventral hernias, as well as 33 inguinal hernias, repaired with an ePTFE patch. In 13 of the ventral repairs, the graft was placed directly over the viscera. During the 18-month follow-up period, there were four recurrences and three infections. None of the patients had clinical evidence of adhesion formation. Moreover, during a reoperation for graft trimming in a patient who had undergone a ventral repair a year earlier, the ePTFE patch was found to have formed a posterior lining that could not be visually differentiated from normal peritoneum. There were no adhesions to this membrane, which was firmly bound to the graft.

DeBord (6) used ePTFE patches in full-thickness repairs of large ventral hernias in 64 patients during an 8-year period. In the 64 cases, 6 infections and 9 seromas developed postoperatively. One infected patch was treated successfully without removal. Although DeBord and colleagues generally did not attempt to shield intra-abdominal contents from the graft, they had no complications related to adhesions, erosion of the patch, or bowel obstruction.

In the series of Kennedy and Matyas (7), 40 ventral hernias were repaired with an ePTFE patch. With a mean follow-up of 49 months, there was one recurrence, one seroma, one wound infection, and one prolonged gastrocutaneous fistula, which developed in a patient in whom a suture had been placed too close to a gastrostomy tube. There were no other complications caused by adhesions, bowel erosion, or bowel obstruction.

Despite the good results achieved with ePTFE, polypropylene mesh remains the most widely used prosthesis for hernia repair, and some authors (8, 9) have reported success in employing it to repair abdominal wall defects. No randomized, controlled clinical trials comparing the use of ePTFE and polypropylene mesh in the repair of abdominal wall defects have been performed, although they are clearly needed. However, much experimental and clinical evidence indicates that ePTFE has certain advantages over polypropylene with respect to bowel-adhesion, tissue-ingrowth, and infection (10–15).

For example, in studies in rats, Law and Ellis (11) found that the extent of adhesions to ePTFE patches was significantly less ($p < 0.05$) than that of adhesions to polypropylene mesh at 1–8 weeks after implantation. Histologic examination showed that the polypropylene mesh incorporated dense collagen fibers in the presence of a mild foreign-body reaction, that omental adhesions had enveloped the fibers of the mesh and become firmly attached to it, and that mesothelial cells were present in an irregular pattern. In contrast, examination of the ePTFE explants showed that collagen had penetrated the interstices of the ePTFE in a regular pattern, and, most important, that mesothelial cells had appeared in a continuous layer on the surface to form a neoperitoneum.

In a study by Murphy et al. (12), either polypropylene or ePTFE was used to repair full-thickness abdominal wall defects in rats. There was a significant difference ($p < 0.005$) between the two groups with respect to bowel adhesions observed after sacrifice and explantation. Histologic examination of the tissue from the polypropylene group showed chronic inflammatory cells, fibroblasts, and rare giant cells, as well as collagen fibers encapsulating the prosthetic material. In the ePTFE group, there was a focal reaction of giant cells, with fewer fibroblasts and less collagen than in the polypropylene group. Nonetheless, abdominal wall reconstruction with ePTFE resulted in wound strength equal to that obtained with polypropylene mesh.

Clinical problems related to the types of tissue reactions to polypropylene mesh observed in these experimental studies have been well documented. Kaufman et al. (13), for example, described a patient in whom a fecal fistula to the skin developed as a result of incorporation of polypropylene mesh into the splenic flexure of the colon. They advised against using polypropylene in intraperitoneal hernia repairs. Schneider et al. (14) described an erosion of polypropylene into the intra-abdominal organs. In a recent article, Nagy and coworkers (15) reported formation of a fistula as a result of erosion into the small bowel and colon in 3 of 4 patients in whom polypropylene mesh had been used for abdominal wall closure. Two of the three fistulas in our series occurred after removal of polypropylene following an unsuccessful repair. Nagy et al. have abandoned the use of polypropylene for this application.

One report on an experimental study (16) has claimed that the moderate tissue reaction to ePTFE results in inadequate tissue attachment to the patch and subsequent reherniation. Our clinical experience, and that of others mentioned above, is in sharp contrast to these findings. The apparent discrepancy between our clinical results and the experimental work of Simmermacher et al. (16) may have arisen because of the surgical implantation technique and specimen sampling protocol used by those authors. An implantation method that leaves any dead space overlying the prosthesis will preclude mesenchymal cell attachment and migration onto and subsequently into the interstices of the ePTFE patch. The tissue incorporation process requires intimate and sustained contact between the surface of the implant and the adjacent muscle and fascia. Thus, samples obtained at necropsy from areas in which no such contact occurred will probably show little or no evidence of tissue ingrowth. In addition, normal wound healing and tissue ingrowth may be substantially muted by the presence of sepsis either in the form of an overt wound infection or subclinical wound contamination.

In a review of the literature, Houck and colleagues (17) reported the rate of infection after incisional hernia repairs, with and without a prosthesis, to range from 15% to 45%, and expressed the view that these procedures should be considered "contaminated" for surveillance and reporting purposes. Although any infection is undesirable, our series infection rate of 12% seems low in comparison to these observations. Vascular grafts made of ePTFE have been found to be associated with low rates of infection in *in vitro* studies (18, 19). Moreover, in an investigation of abdominal wall reconstruction in guinea pigs with wounds contaminated with *Staphylococcus aureus* (20), significantly fewer ($p < 0.05$) organisms adhered to ePTFE patches than to polypropylene mesh.

Interestingly, once an ePTFE patch does become infected, it is possible that the nature of the material contains the infection and makes it easier to treat. The node-and-fibril configuration of ePTFE may inhibit rapid and diffuse penetration of bacteria. Organisms may initially remain clustered in a section of the implant, rather than becoming uniformly dispersed throughout the prosthesis. In our series, we successfully treated 3 of the 9 infected patients, thereby avoiding possible morbidity associated with reherniation after patch removal.

In summary, our long-term clinical experience, as well as the findings of others, indicates that prosthetic patches of ePTFE are safe and effective when used in the repair of large abdominal wall defects that cannot be closed primarily. Operative complications with these devices are within acceptable limits, and the reherniation rate is low. Our long-term histologic and ultrastructural studies revealed that ePTFE evokes little foreign body reaction, even after extended periods of implantation, and that it allows tissue ingrowth to produce a strong repair. Our sequential histologic examination of biopsy specimens from an ePTFE patch offered the opportunity to observe the cytological response and progression at the device-tissue interface in a normal patient over the course of time. Our findings suggest that expanded polytetrafluoroethylene patches are an appropriate choice for full-thickness replacement of the abdominal wall.

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Laparoscopic Pelvic Lymph Node Dissection in the Staging of Prostate Cancer

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Abstract

Background: Men with localized prostate cancer who present with high risk features may benefit from determination of pelvic lymph node status by a laparoscopic lymph node dissection prior to definitive therapy.

Methods: One hundred eighty-nine men with a median age of 69 years (range 49 – 80) with T1 – T3 prostate cancer had a laparoscopic pelvic lymph node dissection (LPLND) prior to definitive therapy (radiation or surgery). All patients had a negative bone scan and a computerized tomography of the pelvis prior to the LPLND. In addition, all patients also underwent a seminal vesicle biopsy (SVB) in order to determine the presence of T3c disease. Prostate-specific antigen (PSA) ranged from 1.6 – 190 ng/mL (median 11 ng/mL) and was > 10 ng/mL in 56.6%, Gleason score was ≥ 7 in 46.7%, and 67.8% had clinical stage T2b–T3a.

Results: Of the 189 patients who underwent an LPLND, 22 (11.6%) had a positive dissection. Between 1 and 51 nodes (median 9) were removed per dissection. PSA, clinical stage, Gleason score and SVB results all significantly influenced node findings. Positive nodes were encountered in 26.5% of those with a PSA > 20 ng/mL ($p=0.0002$), in 16.4% with stage T2b–T3a ($p=0.003$), in 20% with Gleason scores 7 – 10 ($p = 0.0006$) and in 38% of men with a positive SVB ($p<0.0001$). Logistic regression analysis with PSA, Gleason score, clinical stage and the results of the SVB demonstrated that a positive SVB was the most significant predictor of node positivity. The overall transfusion rate was 1% (2/189) and median hospital stay was one day. The complication rate for the LPLND was 9% (17/189).

Conclusion: The LPLND is an effective and efficient means of detecting positive pelvic lymph nodes in patients with localized prostate cancer. It should be considered a necessary diagnostic modality in all appropriate patients who may be candidates for curative therapy. **Key Words:** Laparoscopy, prostate cancer, pelvic lymph node dissection, lymphadenectomy.

Introduction

Prostate cancer is the most common non-skin malignancy in men; approximtely 317,000 new cases occurred in 1996 (1). The American Cancer Society estimates the lifetime risk for developing prostate cancer to be 1 in 5. The most likely explanation for the increase in the number of new cases is the aging male population and the widespread use of prostate-specific antigen (PSA) testing (2, 3).

Improvements in both diagnosis and treatments have also coincided with the increase in the number of new cases of prostate cancer. Application of new technology has provided a means of improving diagnostic accuracy in those patients who are at risk for extra prostatic disease, thus permitting better identification of those patients who would benefit most from curative therapy.

The field of minimally invasive technology has also advanced to include assessment of pelvic lymph nodes in those patients with prostate cancer who may be at high risk for lymph node metastases. Previously, when a patient with localized prostate cancer was a candidate for curative therapy, he was offered an open pelvic lymph node dissection as a means of determining if micrometastases were present. This open dissection was done either at the time of radical retropubic prostatectomy or prior to either perineal prostatectomy or radiation therapy. The laparoscopic pelvic lymph node dissection (LPLND) has mostly replaced the need to perform an open dissection in those patients at risk for pelvic lymph nodal disease (4 – 11). Herein we describe our technique, review our results and describe our indications for performing an LPLND in men with localized carcinoma of the prostate.

Materials and Methods

One hundred eighty-nine men with a median age of 69 years (range 49 – 80) with T1 – T3

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prostate cancer had an LPLND prior to definitive therapy (radiation or surgery). The patients were staged by the TNM system and all had negative bone scan and computerized tomography of the pelvis prior to the LPLND. In addition, all patients also underwent a seminal vesicle biopsy (SVB) to determine the presence of T3c disease. The technique and indications for an SVB have been previously reported (10, 11). Prostate-specific antigen (PSA) ranged from 1.6–90 ng/mL (median 11 ng/mL) and was > 10 ng/mL in 56.6%. Gleason score was ≥7 in 46.7% and 67.8% had clinical stage T2b–T3a disease (Tables 1–3).

TABLE 1

Distribution of Patients Based upon Presenting Prostate-Specific Antigen (PSA) Values.

PSA Range ng/mL	n* (%)
0–4	14 (7.4)
4.1–10	68 (36.0)
10.1–20	58 (30.7)
> 20	49 (25.9)
Total	189 (100)

* n = number of patients

TABLE 2

Distribution of Patients by Gleason Scores.

Gleason score	n* (%)
2–4	28 (14.8)
5–6	71 (38.5)
≥7	90 (46.7)
Total	189 (100)

* n = number of patients

TABLE 3

Distribution of Prostate Cancer Cases by Clinical Stage.

Clinical stage	n* (%)
T1b	5 (2.6)
T1c	18 (9.5)
T2a	38 (20.1)
T2b	86 (45.5)
T2c	35 (18.5)
T3a	7 (3.8)
Total	189 (100)

* n = number of patients
T1b: > 5% of transurethral prostatectomy specimen containing cancer
T1c: PSA-detected tumor
T2a: less than 1/2 lobe involved
T2b: one lobe involved
T2c: both lobes involved
T3a: unilateral extension outside of prostate

The LPLND was performed under general anesthesia by one surgeon using the transperitoneal technique placing 4 trocars in a diamond pattern in the lower abdomen (10, 11). A 10-mm trocar was placed just below the umbilicus after insufflation to 14 mm Hg with CO_2. Two 5-mm trocars and one 10-mm trocar were then placed under direct vision lateral to the rectus fascia and just above the pubis, respectively. The table was then rotated, placing the operative side up, and the procedure was begun by incising the posterior parietal peritoneum overlying the common iliac artery caudal to just lateral to the umbilical ligament. The vas deferens was then isolated and divided between endoclips. This allowed access to the obturator space and the obturator and hypogastric nodal tissue. All of the tissue bounded by the underside of the external iliac vein laterally, the pubis caudally, the obturator nerve and vessels posteriorly, and the common iliac artery cranially was removed. This tissue was then sent for frozen section analysis (for clinically suspicious nodes) and for permanent section analysis. Patients were admitted following the node dissection and fed a regular diet the night of surgery. In most cases, patients were discharged the next day.

Differences in proportions were tested using the Pearson Chi square test. Logistic regression analysis was used to test the effect of multiple variables.

Results

Of the 189 patients who underwent an LPLND, 22 (11.6%) had a positive dissection. Between 1 and 51 nodes (median 9) were removed per dissection. PSA, clinical stage, Gleason score and seminal vesicle biopsy results all significantly influenced node findings. Positive nodes were encountered in 26.5% of those with a PSA > 20 ng/mL ($p = 0.0002$), 16.4% with stage T2b–T3a ($p = 0.003$), 20% with Gleason scores 7–10 ($p = 0.0006$) and in 38% of men with a positive SVB ($p<0.0001$) (Table 4).

Logistic regression analysis using PSA, Gleason score, clinical stage and the results of the SVB as continuous variables demonstrated that only a positive seminal vesicle biopsy significantly predicted node positivity (Table 5).

The length of time needed to perform an LPLND decreased significantly as more experience was gained with the procedure. The mean operative time was 1 hour and 15 minutes (range 15 minutes to 3 hours). Blood loss also significantly decreased with greater experience. The

TABLE 4
Likelihood of Encountering a Positive Laparoscopic Pelvic Node Dissection.

Variable		Positive n* (%)	Negative n* (%)	p Value
PSA (ng/mL):	1–20	9 (6)	131 (94)	
	> 20	13 (26.5)	36 (73.5)	0.0002
Gleason score:	2–6	4 (4)	95 (96)	
	7–10	18 (20)	72 (80)	0.0006
Stage:	T1b–T2a	1 (1.7)	60 (98.3)	
	T2b T3a	21 (16.4)	107 (83.6)	0.003
SVB:	negative	6 (4)	141 (96)	
	positive	16 (38)	26 (62)	< 0.0001

* n = number of patients

Prostate-specific antigen (PSA)
Gleason score, clinical stage
Seminal vesicle biopsy (SVB)

TABLE 5
Multivariate Analysis of Results of Seminal Vesicle Biopsy (SVB), Prostate-Specific Antigen (PSA), Gleason Score and Clinical Stage Compared to Lymph Node Dissection.

Variable	p Value
SVB	< 0.0001
PSA	0.07
Gleason Score	0.06
Clinical Stage	0.08

TABLE 6
Complications Associated with Laparoscopic Lymph Node Dissection.

Complication	n* (%)
penile and scrotal edema	11 (5.8)
peripheral edema	5 (2.6)
urinary retention	3 (1.6)
obturator nerve palsy	2 (1)
pelvic hematoma	2 (1)
high inspiratory pressure	1 (0.5)

* n = number of patients
No patients required a laparotomy.

average blood loss was 30 cc with a range of 10–250 cc. In the first 50 patients, one unit of autologous blood was taken prior to the procedure. Two patients (4%) were given their unit back. In the next 139 patients, no autologous blood was taken and no patients received a transfusion. The overall transfusion rate was 1% (2/189).

A total of 17 (9%) complications occurred in these 189 patients (Table 6). The most common complication, occurring in 11 patients, was edema of the penis and scrotum. Two patients (1%) required readmission for infected pelvic hematomas. All node dissections were completed and no patients required a conversion to an open dissection. No patients required a laparotomy because of complications. There were no deaths associated with the LPLND.

Discussion

Treatment for localized carcinoma of the prostate is dependent on the extent of disease at the time of diagnosis. Patients who appear to have clinically confined disease may be candidates for surgery (radical prostatectomy) or radiation therapy (external beam irradiation or interstitial therapy). Definitive therapy for patients with either T3c (seminal vesicle) or N+ (pelvic lymph nodes) disease may be only marginally beneficial (12–16). Thus, controlling the primary disease may not affect the subsequent development of distant metastases in these patients (17–22).

Prior to the advent of laparoscopic surgery, patients who presented with high risk features for nodal disease had to undergo an open retropubic lymph node dissection in order to confirm that they would be candidates for curative therapy. Pathologic confirmation of lymph node status was required because of the inaccuracy of radiographic staging. In a recent review of the results of CT scanning prior to radical prostatectomy in 173 patients, CT understaged 75% of the patients with positive nodes (23). CT scanning was found to benefit only those with a PSA of at least 20–30 ng/mL.

Because of the inadequacy of radiographic staging, a lymph node dissection was often done at the time of radical retropubic prostatectomy in those patients electing surgery as their treatment option. For those with a positive node dissection, the radical prostatectomy was often abandoned and the patient closed. Patients with high-risk disease experienced unnecessary surgery and morbidity if the nodes were positive.

In patients undergoing a node dissection followed by radical prostatectomy, the prostate is removed if the frozen section is negative. However, in up to 85% of the patients, the frozen section analysis of the nodal tissue at the time of the radical prostatectomy is falsely negative and a non-curative prostatectomy is performed (24–26). In these patients, where accurate determination of nodal status is critical, a minimally invasive surgical procedure could correctly identify those patients best treated with curative therapy and possibly prevent an unnecessary prostatectomy.

The surgical procedure used to remove the pelvic nodal tissue with laparoscopy has been found to be as effective as the open techniques.

Data from centers performing laparoscopic pelvic node dissections have demonstrated similar results (number of nodes removed and node positivity) as the open retropubic pelvic lymph node dissection (4–11). Rukstalis et al. (27) performed LPLND on patients with clinically localized prostate cancer. In 20 patients, this was followed by an open lymph node dissection with removal of the remaining lymph nodes in the dissection area. Using this method, he found that the LPLND was able to remove 87–95% of the desired lymph nodes. In the present study, a median of 9 nodes was removed, data that are consistent with other reports in the literature.

The data from this study also demonstrate that not all patients need to have their lymph nodes evaluated. While the overall node positivity rate was 11.6%, patients with low risk features were unlikely to have a positive dissection. Patients with PSA < 20 ng/mL, Gleason score < 7, lesions T2a or less or those with a negative SVB had only a 6%, 1.7%, 4% and 4% likelihood respectively of having a positive dissection. These patients can be adequately treated by either surgery or radiation, without the need for pathologic nodal assessment.

Those patients who present with high risk features should undergo a pelvic lymph dissection. Partin et al. (28) evaluated 1,058 men who had radical prostatectomy and open staging pelvic lymphadenectomy and reported 11% node positivity. Using this information, they were able to construct treatment algorithms based upon the pretreatment variables and assign probabilities of the likelihood of a positive node dissection.

The data from our study also yields similar probabilities. Patients who present with a PSA > 20 ng/mL, a Gleason score ≥7 or stage T2b–T3a had a 26.5%, 20% and 16.4% likelihood respectively of having a positive dissection. While the probabilities in the two studies are similar, there is one major difference. All of the patients examined in Partin's study had an open node dissection with or without prostatectomy (depending on the frozen section analysis). The patients in our study only had an LPLND and those with positive nodes did not have open surgery and subsequent radical prostatectomy or radiation. Consequently, 22 of our patients were spared an unnecessary treatment. A similar approach in Partin's study would have spared 111 patients the need for the additional surgery.

In addition to the pretreatment risk factors, PSA, Gleason score and stage, we also analyzed the contribution of the SVB. Patients with a positive SVB had a 38% likelihood of having a positive dissection. In fact, a logistic regression analysis revealed that the SVB was superior to the other variables in predicting for a positive pelvic lymph node dissection. These results were also confirmed by a study by Mukamel et al. (29) which found that 43% of patients with seminal vesicle involvement had pelvic nodal disease on open pelvic lymph node dissection. Vallancien et al. (30) also found that 50% of patients with positive seminal vesicle biopsies had positive pelvic lymph nodes. Thus, it appears that the result of the SVB is also an important prognostic variable.

The LPLND would not be a procedure that could be routinely offered if it were technically difficult to perform or if it were associated with a high complication rate. The data from this study indicate that the procedure can be performed with reasonable operative time and with low morbidity. The operative time ranged from 15 minutes to 3 hours. More than half of the cases were completed in less than 1 hour and 15 minutes, and no cases were terminated prematurely. The median blood loss was 30 cc and hospital stay was less than one day in more than half of the cases. These data demonstrate that the LPLND is a reasonable surgical approach that can be performed in a cost-effective and time-efficient manner.

In addition to the operative characteristics, we have also shown that there are few complications associated with the LPLND. The total complication rate was 9%, with the majority of the complications being minor swelling and edema that resolved spontaneously. No patients suffered any permanent complications, and only 2 patients required readmission for an infected pelvic hematoma.

The complication rates in men undergoing open node dissections appear to be far greater than those associated with the LPLND. McCullough et al. (31) compared two groups of men having pelvic lymph node dissections and noted complications in those with node dissection alone as well as in those who had simultaneous radical prostatectomy. Twenty percent of those who had node dissection only and 30% who had both node dissection and prostatectomy had complications. Herr (32) also evaluated the morbidity of the node dissection in men undergoing simultaneous retropubic prostate seed implantation. He reported a 16% incidence of complications, which included wound infection, lymphocele and pelvic abscess.

We conclude that patients who present with a positive SVB, elevated PSA above 20 ng/mL, stage T2b or greater, or Gleason score ≥7 should be considered candidates for an LPLND. In such cases, the LPLND is an accurate and safe means of correctly identifying those patients with localized prostate cancer who would be the best candidates for curative therapy.

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The Impact of Laparoscopic Surgery in the Management of Adnexal Masses

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Abstract

The objective of this study is to evaluate the clinical aspects of laparoscopic management of adnexal masses. The feasibility of this approach has been demonstrated, but the safe and effective use of laparoscopy for this indication requires training, technical skills and experience on the part of the laparoscopist. If used appropriately, many patients will benefit from minimally-invasive surgery.

We compared clinical factors of patients having laparoscopy to those having laparotomy in a case-control study of 30 patients with adnexal masses. Oophorectomy or ovarian cystectomy was performed by laparoscopy for 20 women and by laparotomy for 10 women. Comparing the 2 groups, the most significant difference was the decrease in length of hospital stay in the laparoscopy group. There were no significant differences in operative time or intraoperative complications. Estimated blood loss was lower in the laparoscopy group, and no intraoperative complications occurred. No patient required conversion from laparoscopy to laparotomy. All patients had benign disease despite the inclusion of patients with risk factors for ovarian carcinoma.

This study clearly demonstrates the clinical benefits of laparoscopic management of adnexal masses treated with oophorectomy or ovarian cystectomy. **Key Words:** Laparoscopy, adnexectomy, ovarian carcinoma.

Introduction

Advances in laparoscopy have allowed physicians to perform procedures previously accomplished only by laparotomy. Gynecologists have utilized laparoscopy for many years in the performance of tubal ligation, evaluation of pelvic pain, and treatment of adnexal cysts. General surgeons now commonly perform laparoscopic procedures including cholecystectomy and appendectomy, and are increasing the number of indications for which it can be utilized. The use of laparoscopy by gynecologic oncologists also promises less invasive techniques for treatment of cancer. Endometrial cancer can now be managed by laparoscopic-assisted vaginal hysterectomy and laparoscopic lymph node sampling. Early-stage ovarian cancer may be staged laparoscopically, and cervical cancer can be managed with laparoscopic pelvic and aortic lymphadenectomy and radical vaginal hysterectomy.

Several studies have demonstrated the feasibility of operative laparoscopy in the treatment of adnexal masses (1–4). The same surgical principles that apply in laparotomy must apply to laparoscopy. Given the possibility of encountering malignant adnexal masses, careful preoperative consideration must be used. Preoperative counseling must include the possibility of laparotomy and staging procedures if a malignancy is diagnosed on frozen section. Cytologic washings must be collected at the initiation of the procedure. The pelvis as well as upper abdomen must be visualized and described. Techniques to prevent spillage of cyst contents include use of laparoscopic endobags and aspiration of large cysts using the endoscopic cyst aspirator set. All adnexa must be sent for frozen section histologic evaluation to allow for immediate management of malignancies. Strict application of these guidelines will lead to uncompromised treatment of

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patients with ovarian cancer, and patients will reap the benefits of laparoscopic surgery.

Clinical benefits of the laparoscopic approach have included decreased morbidity, improved cosmetic results with smaller incisions, and faster return to normal activity. It is our goal to objectively demonstrate clinical benefits and therapeutic efficacy using a case-control study of laparoscopy compared to laparotomy in the management of adnexal masses.

Materials and Methods

We identified two 12-month academic years, July 1, 1990–June 30, 1991 and July 1, 1993–June 30, 1994, separated by a 24-month period during which we analyzed all cases involving operative laparoscopy or laparotomy for resection of adnexal pathology by oophorectomy (with or without salpingectomy) or ovarian cystectomy. All surgery was performed by 3 gynecologic oncologists at the Mount Sinai Hospital in New York. A database of all patients admitted to the service was compiled from three independent sources of admission data: (1) computerized hospital records of patient admissions and discharges indexed by attending physician and by service, (2) divisional databases, and (3) fellow case logs. Data was extracted from the above-mentioned sources including: age, menopausal status, preoperative diagnoses, pathology reports, surgical procedure, complications, intraoperative blood loss, operative time, number of prior operative procedures, length of hospital stay, occurrence of postoperative nausea and requirements for postoperative pain medication. Statistical analysis utilized Student's t test.

Results

The case group consisted of 20 patients who underwent laparoscopy. The control group consisted of 10 patients who underwent laparotomy. All patients had an admitting diagnosis of adnexal mass.

Preoperative assessment included: medical history, physical exam, radiographic studies and/or measurement of CA-125 serum marker.

Age range in the laparoscopy group was 22–72 years, with a mean of 52 (±14) years, the majority being postmenopausal. The laparotomy group ages ranged from 17–76 years with a mean of 37 (±17) years, with all but 2 of the patients being premenopausal. The mean ages of the patients in the two groups were significantly different (p = 0.02).

The preoperative diagnosis for both groups included adnexal mass, either simple or complex, and all patients had benign findings intraoperatively. Pathologic diagnosis included serous cystadenoma (8), dermoid cysts (6), thecomas (4), simple cysts (3), mucinous cystadenomas (2); tubal CIS (1) serous cystadenofibroma (1), Leydig's cell tumor (1), paratubal cysts (1), ovarian dysplasia (1), hemorrhagic corpora luteal cysts (1), and endometrioma (1). Table 1 shows the specific procedures performed in each group. The laparotomy group underwent 6 unilateral adnexectomies, 2 bilateral adnexectomies, and 2 ovarian cystectomies. The laparoscopy group underwent 6 unilateral adnexectomies, 12 bilateral adnexectomies, and 2 ovarian cystectomies. No cases required conversion from laparoscopy to laparotomy, and no intraoperative complications occurred.

Comparisons between the 2 groups for selected clinical characteristics are shown in Table 2. Estimated blood loss ranged from 75–200 cc in the laparotomy group with a mean of 118 (±48 cc), and 10–100 cc in the laparoscopy group with a mean of 41 (±27) cc; this difference is significant with p = 0.0005. Operative time ranged from 36–140 minutes in the laparotomy group with a mean of 85 (±33) minutes, and 40–251 minutes in the laparoscopy groups with a mean of 107 (±58) minutes. This difference is not significant (p = 0.2).

TABLE 1
Types of Surgery Performed for Management of Adnexal Masses

	Laparoscopy	Laparotomy
Cystectomy	2	2
USO	6	6
BSO	12	2
Total	20	10

USO = unilateral salpingo-oophorectomy; BSO = bilateral salpingo-oophorectomy.

TABLE 2
Comparison of Clinical Aspects Between Laparoscopy and Laparotomy Groups

	Laparoscopy mean ± SD	Laparotomy mean ± SD	p-value
Age (years)	52 ± 14	37 ± 17	0.02
Estimated blood loss (mL)	41 ± 27	118 ± 48	0.0005
Operative time (minutes)	107 ± 58	85 ± 33	0.2
Length of stay (days)	1.2	6	<0.0001

The size of the masses approached with laparoscopy was variable, the largest being 13 x 9 x 3 cm, a benign cystic teratoma which was morselated and removed in endobags. The smallest was a benign ovarian cyst measuring 2 x 2 x 2 cm. The average volume was 69 cm^3 and 274 cm^3 in the laparoscopy and laparotomy groups, respectively (data not shown).

All patients received parenteral narcotics postoperatively for pain control in the laparotomy group. Patients in the laparoscopy group rarely required parenteral narcotics in the postoperative period; in fact, most required only oral analgesics. We recorded the incidence and timing of postoperative nausea in the laparoscopy group and found only 2 patients with significant complaints, one of whom required overnight observation due to her symptoms. The second patient had a history of significant nausea and vomiting during a prior procedure, but despite the use of droperidol and metoclopramide in the perioperative period, she had nausea and vomiting within the first 8 hours following surgery.

Length of stay was the most significant difference found between the 2 groups. Average hospital stay was 1.2 days for the laparoscopy group, as compared to the laparotomy group, whose average stay was 6 days ($p < 0.0001$). The study cases were collected when laparoscopy was first initiated. With experience, we have realized that hospital admission for postoperative care is rarely necessary and currently the majority of patients with laparoscopic adnexectomies are discharged from the recovery room 4–6 hours postoperatively. Although we did not document time to full recovery, the data that were available suggest that women treated with laparoscopy returned to normal and productive activity more quickly.

Discussion

Laparoscopy is widely used in gynecologic practice. This study supports other studies showing that innovative use of advanced operative laparoscopic techniques accomplishes equal or improved therapeutic results with less morbidity than standard surgical procedures. With liberal use of ultrasonography, an increased number of patients, both reproductive and postmenopausal, are being referred to gynecologic oncologists. These women will benefit from the use of laparoscopy when managed by a well-trained and experienced surgeon.

The use of operative laparoscopy to perform adnexectomies is feasible, yet its use in managing postmenopausal patients and potentially malignant masses has been less accepted (5–8). Some fear suboptimal treatment and spill of malignant cells in the presence of an ovarian carcinoma. Treating postmenopausal patients with bilateral adnexectomy alone has also been criticized because standard therapy has included hysterectomy in the presence of a benign ovarian mass (9). With informed consent this may be unnecessary, as most adnexal masses in postmenopausal women are benign and the rate of subsequent malignancy in the remaining organs is low.

In this study of 30 patients, we did not exclude women with a family history of ovarian cancer, elevated CA-125, or features suggestive of malignancy on radiologic studies. Despite the referral bias of a gynecologic oncology practice, no patient was found to have malignant disease. Nevertheless, all patients were approached with an index of suspicion.

Washings were collected with a suction irrigator at the beginning of all procedures. The pelvis, upper abdomen, and diaphragm surfaces were clearly visualized. All masses were approached with care to prevent spillage by the use of laparoscopic endobags. In the event of cystic masses too large to fit into an endobag, the endoscopic-cyst aspirator was used to puncture and drain the cyst without spillage, decompressed, and the specimen placed directly into an endobag for removal. We have found this to be a very successful approach to large cystic masses. The use of endobags also prevents contact of the mass with the abdominal incision, thereby decreasing the risk of tumor seeding along the trocar tract. Once the adnexa or cyst was removed, it was sent immediately for frozen section. Had a malignancy been found, it could be addressed at that time with staging via laparotomy, or by laparoscopic staging. All patients signed consents for possible laparotomy and staging procedures; therefore, in the event of a malignancy there would be no delay in therapy.

The results of this study demonstrate several clinical benefits of laparoscopy. Although estimated blood loss was small in both groups, there was a significant decrease in the laparoscopy group, likely due to the lack of a large abdominal incision. Operative times were not significantly different. Of note, most laparotomies involved unilateral adnexectomies, whereas the laparoscopy groups had mostly bilateral adnexectomies given their postmenopausal status. Therefore, the laparoscopy group had equivalent operative times despite the higher frequency of bilateral adnexectomies. As the operating room staff and surgeons become more experienced, the operative time for laparoscopy may be even shorter than for laparotomy. Postoperative pain control in the laparoscopy group consisted mostly of oral analgesics, whereas the laparotomy group invariably required parenteral narcotics. In addition, the postoperative recovery period was much shorter for the laparoscopy group. Currently, patients undergoing laparoscopic adnexectomies are discharged from the recovery room on a same-day basis. Patients also benefit from more rapid return to normal activity and a better cosmetic result with only small incisions. In this study, there were no negative effects of laparoscopy, no need for conversion to laparotomy, and no significant complications or resulting inadequate treatment.

Since the time when we collected these cases for study, we have encountered 5 cases of early-stage ovarian carcinoma during laparoscopic oophorectomy and completed laparoscopic staging with laparoscopic assisted vaginal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and bilateral pelvic and aortic lymphadenectomy. The operative assessment was complete with excellent visualization of the upper abdomen and diaphragmatic surfaces, and complete pathologic specimens were obtained. Several groups have also reported the feasibility of successful staging of Stage I and II ovarian carcinoma (10–12).

The ability to use laparoscopy as a tool in managing adnexal masses allows early treatment that is therapeutically sound and offers the clear benefits of decreased hospital stay, decreased cost, and earlier return to normal activities.

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Commentary

New Medicine for the New Millennium

James F. Holland, M.D.

Fellow Students:

Now that you have limbered up by successfully completing medical school, you are ready for the main event — being a doctor for life. And what a life it will be! You will enjoy a special role in society — in every culture of the world — because you have a special calling. Yours is the task to fend off death, to reduce pain and suffering, and to improve the quality of life. It is not likely that these activities will change by January 1, 2000, as we enter the third millennium, when most of you will still be enjoying on-the-job training.

But what then? Most of us in this waning century have perceived medicine as a doctor-patient relationship, one on one. There is a change in the electronic wind, I believe, that will alter your role. When a click of your mouse can link Brooklyn to Beijing, Buenos Aires or Berlin, you know that the Internet will change your life. The world was not preshrunk. The process of shrinking the globe has begun in earnest in the World Wide Web. Real time communication does not bring virtual reality, it brings the genuine article, real reality to your very desktop. Your medicine will be a doctor–world relationship, one on one.

We are the world's richest and most powerful nation. We should export four of our best products: health, education, government with the consent of the governed, and a stable economy with its better standard of living. I believe we must do so, and as doctors, I believe you must be in the forefront, if not the leadership, of this enterprise. These are not widgets for export. They are the substance from which global glue is made, cementing the human race together so that life is meaningful everywhere on the planet. If life becomes meaningless in desolate areas of the earth, the third millennium will be a thousand years of turmoil.

Take health. A vast and expanding underclass in the world still lives in squalor. They drink from rivers and ponds, from rivulets and puddles, they eat poorly and not enough, and they lose nearly half their young children from diarrhea, malnutrition, malaria and preventable causes of death. Starving the brain in infancy and early childhood, like starving the body, leads to stunted growth.

Fundamental health starts with sanitation and nutrition. Agricultural scientists who improve on the yield and protein content of the indigenous crops of Asia and Africa labor mightily for half the world's population. They are our allies. Inventors and engineers who create and simplify water purification systems are colleagues in the quest for health. Relatively speaking, vaccines are cheaper than disease. One of the world's great triumphs is the total elimination of smallpox by worldwide vaccination. Measles, hepatitis B and other preventable diseases claim untold thousands of lives each year, needlessly, for lack of an aroused world and a functioning infrastructure to conduct immunization.

Can we export education? In villages where light comes from the sun and the fireside, where electricity is still a far-off dream, the hand-cranked radio has been a magical instrument of learning. First, learning that there is an outside world. Illiteracy is a correctable blot on humanity, and its persistence at all in the United States is a blemish on America's luster. How is a man in a developing country going to develop himself or his country if he can't read? How is a woman going to manage her reproductive life, her family, her personal development and her attainment of equality if she is denied access to the accumulated wisdom in books? Television, that great hope of education, has in large part dawdled along the path, to stuff us in America like a Strasbourg goose, with sitcoms, soap operas and advertising fluff. To be sure, there is an occasional station that provides cultural and educational fare suitable for intellectual stimulation. The sad part is not how bad it is, but how good it could have been. But wait — the computer and the Internet to the rescue. They will soon own the educational horizon.

In the third millennium, forget the laptop. On your wristband computer, you may get to see a total viscerectomy, bloodless, of course, followed by implantation — since transplantation will be a thing of the past. Techniques of growing one's own cells into new organs will be commonplace if gene thera-

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Key Words: New medicine, millennium, internet, world wide web.

pies have not already normalized organs in situ. Universal parts will be available for those who can't afford (or whose HMOs won't pay for) custom organ design. But to make certain that the world does not get overpopulated by individuals with ancient chassises and souped-up replacement parts, the Internet will periodically offer "Do It Yourself Visceral Exchange Kits," payable in advance, naturally.

Neither health nor education can flourish in anarchy. Government is necessary, and to be ultimately successful the consent of the governed is needed. In bloody wars, health and education are early sacrificial victims. War implies chaos, starvation, disease and death often far worse for civilian populations than among the military itself. Is it too much to ask doctors to study war? War impacts on human health in a big way. Tens of millions have died in wars over the ages, yet this special human failing gets scant medical attention.

Is the world so politically stable that we can be assured that weapons of mass destruction will never be used? The awesome power of nuclear weaponry seems to have been downgraded in foggy memory. A single high level blast could ignite the forests of Montana, Idaho, Washington and Oregon into a pyromaniac's dream candle to light the world. A single ground level hit on Manhattan would make Buffalo the largest city in the Empire State — for a few minutes. Can't doctors fathom the intricacies of the human mind in order to prevent such grievous behavior? The study of the brain and its functions, and dysfunctions, is a high calling. Our thought processes are our most distinctive feature as a species. Many politicians in the past have had an intellectual and emotional disconnect from the realties of all-out war. It could be true again in the future.

You young doctors can do better. There won't be a pill that averts war. But there can be a universal chorus of doctors from every nation who know life and death more intimately than others, chanting like the chorus in ancient Greek tragedies about the catastrophes to come. And you can sing of the nobility of life well invested, with health, education and a future. War and its consequences are too important a problem today and for the third millennium to be off your screens. Every day every doctor should ponder the human condition and how to avoid the tentacles of war.

Stable consensual government also is indispensable for justice and for broad economic security. A meaningful job is part of the fulfillment of life. With work comes satisfaction and the resources to supply oneself, one's family and one's society with a quality existence. Doctors rarely have to worry about this for themselves. It does not require a Rolls Royce to get to the office. But there are many people in this world who lack employment, and thus often lack good nutrition and good health, good or any education, and certainly lack a good quality of life. Such understandably unsatisfied people are the raw material of discontent, of crime, and of revolution, becoming a rabble in arms. As we survey our appropriate obligations to fellow Americans, we disregard at our own peril, equally appropriate obligations to globe mates who are but a mouse click or an airport away. They are so close we will probably import many of their epidemic diseases, and not a few of their problems.

The industrial revolution and motor vehicular traffic have so depended on fossil fuels that CO_2 production has led to a greenhouse effect, and evidence of global warming. Would nuclear power with all its problems be better? Shouldn't we all lobby for more research on the fusion reactor, which could provide unlimited energy from the hydrogen in water? And what of industrial and agricultural pollution that fouls the air and poisons the aquifer? Shouldn't we admit a finite limit for the human population, before derivative industrial pollution, primitive territoriality epidemics or famine evoke their own kind of population control?

Well, those are near-term questions with which your generation must grapple. Your productive careers will span the next 50–70 years. Many of you will still be sprightly in your 90s, and if the current politics of medical economics prevail, many will still be working. The first half of the 21st century will certainly be an interesting time. In our prophecies we usually underestimate badly. In 1900, not many prophets foresaw men on the moon, women in space, instant communication, hundreds of millions of mathematical calculations per second, antibiotics, heart transplants, the rise of cancer, and the disappearance of tuberculosis sanitoria and insane asylums.

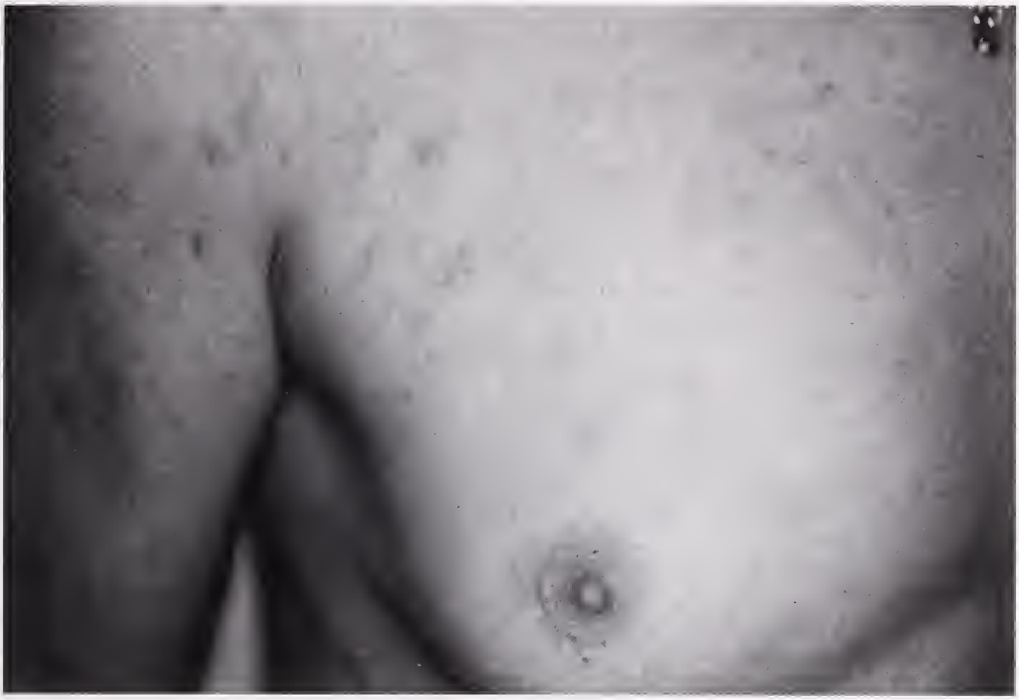
Medicine stands now on the threshold of a phenomenal advance. The complete delineation of the human genome by 2005 will allow physicians to define the interaction of the environment with the unique nature of each individual's operating system. You will not only be able to predict disease, but may be able to intervene to prevent it. Yea, the glory days of medicine are still ahead.

Since we all cohabit this same tiny speck of the universe, let us be sure we all participate in the work and all partake of the rewards. To bring this about will require that doctors lead in concepts of health, not just disease, entailing commitments to education, governance and economics.

I addressed you at the outset as Fellow Students. It is my fervent hope that when you reach your 50th anniversary of graduation from medical school, which I celebrated two days ago, you can be as confident of the future of medicine in the third millennium as I am that each of you can be a powerful and magnificent force for the betterment of your patients, and of the world.

Dermatology Notes

Cirrhosis



CUTANEOUS MANIFESTATIONS OF CIRRHOSIS include a petechial eruption resulting from thrombocytopenia associated with hypersplenism. Gynecomastia is another manifestation of this patient's hepatic cirrhosis.

—Jacob Baral, M.D. and Mark Lebwohl, M.D.

Abstracts

*The following abstracts were presented by investigators at the Sixteenth Annual Samuel Bronfman Department of Medicine Research Day at Mount Sinai School Medical Center. Most of the investigators serve in the Samuel Bronfman Department of Medicine including those working at affiliated institutions such as The Jewish Home and Hospital, New York, NY; The Bronx Veterans Affairs Medical Center, Bronx, NY; Elmhurst Hospital Center, Elmhurst, NY; Queens Hospital Center, Jamaica, NY; Englewood Hospital and Medical Center, Englewood, NJ; and St. Joseph's Hospital and Medical Center, Paterson, NJ. Four abstracts identified with an * were awarded special prizes on Research Day. Several additional reports were presented or shown, but the abstracts have been published elsewhere. All others were presented as posters. Abstracts from Queens Hospital Center were presented as posters on Research Day held at that institution.*

Research in Medicine 1998
Mount Sinai School of Medicine

Alcohol Research

Polyunsaturated Phosphatidylcholines (PC) Protect Plasma Low Density Lipoproteins from Oxidation. K.P. Navder[1], E. Baraona[1,2], and C.S. Lieber[1,2]. [1]Alcohol Research Center, Bronx VA Medical Center, Bronx, NY; and [2]Department of Medicine, Mount Sinai School of Medicine, New York, NY.

A prevailing hypothesis for atherosclerosis development involves the oxidation of Low Density Lipoproteins (LDL). Soybean derived polyenylphosphatidylcholine (PPC), and its 2 main components have shown "antioxidant" effects in several models of oxidative stress. To assess whether the main components of PPC affect the oxidizability of LDL, plasma from 9 healthy volunteers was incubated *in vitro* with either 10 μM dilinoleoyl PC (DLPC) or 10 μM palmitoyl-linoleoyl PC (PLPC); and their effects were compared with 10 μM distearoyl PC (DSPC), a saturated phospholipid, and with 1 mM α-tocopherol, a recognized antioxidant. Oxidation was initiated by the addition of 5 μM Cu^{2+} sulfate and monitored for the production of conjugated dienes. The lag phase (indicating the resistance of LDL to oxidation) was longer ($p < 0.001$) for LDL incubated with DLPC (132%) or PLPC (135%), but not with DSPC. This effect was similar to that of 1 mM α-tocopherol (135%). LDL oxidation was also initiated with 2.2'-azobis (2-amidinopropane) dihydrochloride, a free radical initiator, and monitored by the changes in O_2 consumption. The inhibition time (reflecting the antioxidant content of LDL) was also longer ($p < 0.001$) for DLPC (188%), PLPC (188%) and α-tocopherol (206%), but not for DSPC.

In Conclusion, we demonstrate that both DLPC and PLPC, the main phospholipid species of PPC, are extremely effective in opposing LDL oxidation, and should be considered in the treatment of atherosclerosis.

Attenuation of Lipopolysaccharide-Induced Tumor Necrosis Factor-alpha Production in Rat Kupffer Cells by Dilinoleoylphosphatidylcholine. C.M. Oneta[1,2], K.M. Mak[1,2], and C.S. Lieber[1,2]. [1]Alcohol Research Center, Bronx VA Medical Center, Bronx, NY; and [2]Department of Anatomy, Mount Sinai School of Medicine, New York, NY.

Polyenylphosphatidylcholine (PPC) protects against the development of fibrosis and cirrhosis in alcohol-fed baboons. Furthermore, dilinoleoylphosphatidylcholine (DLPC), its main constituent (40–52%), decreases the *in vitro* activation of hepatic stellate cells and opposes the oxidative stress induced by arachidonate in Morris hepatoma cells. Moreover, activation of Kupffer cells (KC) by gut-derived lipopolysaccharides (LPS) leads to an enhanced production of cytokines. Among these, tumor necrosis factor (TNF)-α has been implicated in diverse metabolic complications leading to hepatotoxicity. The aim of this study was to evaluate whether DLPC also affects KC and attenuates the *in vitro* production of TNF-α. For comparison, palmitoyl-linoleoylphosphatidylcholine (PLPC), the other major component of PPC (23–24%), and distearoylphosphatidylcholine (DSPC), the saturated counterpart of DLPC, were also tested. KC from Purina chow-fed rats were isolated by Percoll density gradient centrifugation after digestion with collagenase. KC were then seeded onto plastic Petri dishes and kept in serum-free RPMI-1640 medium containing either 10 μM of DLPC, PLPC or DSPC (dissolved in 0.05% albumin) in the presence or absence of LPS (1 μg/mL). After 20 hours in culture, the media were collected and ultrafiltrated for TNF-α measurement by enzyme-linked ummunosorbent assay (ELISA). KC were harvested and their DNA was determined by fluorometry. KC viability was 80–90%. Treatment of KC with DLPC or albumin alone had no effect on TNF-α production, compared to untreated KC (10.2 ± 1.6 and 9.7 ± 1.8 vs 10.2 ± 1.5 pg/ng DNA, $n = 6$). LPS stimulated TNF-α production by 62% (15.7 ± 2.7 vs 9.7 ± 1.5 pg/ng DNA in albumin, $p < 0.01$, $n = 6$). Addition of DLPC to the LPS-activated KC decreased TNF-α production by 23% (12.2 ± 1.8 vs 15.7 ± 2.7 pg/ng DNA, $p < 0.05$, $n = 6$). No effect of PLPC or DSPC on TNF-α a generation was observed.

In conclusion, DLPC selectively decreases the LPS-induced TNF-α production by KC; this effect on cytokines may provide a potent mechanism against liver injury, possibly in association with its antifibrotic and antioxidative actions.

Inducibility of Cytochrome P450 2E1 and 1A1 Activities in Pancreatic Microsomes. I.G. Kessova[1,2], L.M. DeCarli[1,2], and C.S. Lieber[1,2]. [1]Alcohol Research Center, Bronx VA Medical Center, Bronx, NY; and [2]Department of Medicine, Mount Sinai Medical School, New York, NY.

Cytochromes P450 2E1 and 1A1 contribute to the toxicity and carcinogenicity, in various tissues, of ethanol and tobacco smoke, respectively. In pancreas, however, prior studies were disappointing because enzyme activities were much lower than expected from 2E1 and 1A1 contents. This problem was overcome by improving microsomal isolation procedures and using highly sensitive assays for the metabolism of p-nitrophenol (p-NP) and ethoxyresorufin (ER), substrates specific for 2E1 and 1A1. In addition, 2E1 and 1A1 content were estimated with high-resolution chemiluminescent Western blots using recombinant 2E1 and 1A1 as standards. In rats fed ethanol (36% of energy) for 3 weeks, p-NP-hydroxylase activity and 2E1 content increased 3–4-fold, compared to controls pair-fed with isocaloric carbohydrates. In pancreatic microsomes, specific 2E1 activity (expressed per 2E1 content) was similar to that in liver, whereas the 2E1 content was much lower, in both ethanol-fed and control rats. In microsomes of liver and pancreas of ethanol treated rats, there was a significant correlation between p-NP-hydroxylase activity and immunologically determined content of 2E1. Another group of rats was given methylcholanthrene (MC), 40 mg/kg IP in 0.5 mL corn oil, or corn oil alone, for 3 days. MC increased pancreatic microsomal ER-O dealkylation and 1A1 content 61- and 42-fold, respectively.

Conclusion: In pancreatic microsomes, 2E1 and 1A1 contents as well as activities are strikingly increased by ethanol and MC, and may play a role in the pathogenesis of pancreatitis and cancer induced by alcohol and/or smoking.

Incorporation of Polyenylphosphatidylcholine into Pancreatic and Hepatic Phospholipids Provides Protection Against Alcohol-Induced Oxidative Stress. S.I. Aleynik[1], M.A. Leo[1], M.K. Aleynik[1], and C.S. Lieber[1,2]. [1]Section of Liver Disease and Nutrition, Alcohol Research Center, Bronx VA Medical Center, Bronx, NY; and [2]Department of Medicine, Mount Sinai School of Medicine, New York, NY.

We found that polyenylphosphatidylcholine (PPC), a soybean extract, provides protection against alcohol-induced oxidative stress in the liver of nonhuman primates, and preliminary results indicate a similar effect in pancreas. To determine whether this is associated with incorporation of PPC components into these tissues, phosphatidylcholine (PC) species, including 18:2 – 18:2 PC (DLPC), the main constituent of PPC, were measured by high-pressure liquid chromography (HPLC) and gas chromography-mass spectroscopy (GC/MS) in rats fed adequate liquid diets rich in vitamin E (30 IU/1000 cal) and containing PPC (3 g /1000 cal or equivalent amounts of linoleic acid such as triglycerides in safflower oil, control) with either ethanol (36% of energy) or isocaloric carbohydrates for 2 months. Compared to control, PPC significantly increased DLPC content in hepatic (204 ± 19 vs 124 ± 8 nmol/g; $p < 0.05$) and pancreatic (1120 ± 220 vs 320 ± 9 nmol/g; $p < 0.001$) phospholipids. Similar results were obtained when values were expressed per protein or total phospholipids. Alcohol tended to decrease DLPC in pancreas, but when PPC was added to the ethanol, it restored the levels to above of that of in control. There was a similar effect of PPC on hepatic and pancreatic OLPC (18:1 – 18:2 PC), another species of PPC, whereas SAPC (18:0 – 20:4 PC) and PAPC (16:0 – 20:4 PC), which are primarily endogenous PC species, were not significantly affected by PPC. They both were decreased after alcohol in liver as well as pancreas. The greater effect of PPC on pancreatic than on hepatic phospholipids may reflect a correspondingly more rapid phospholipid turnover. While alcohol induced a significant oxidative stress, 4-hydroxynonenal (4-HNE) and F_2-isoprostanes (F_2IP) measured by GC/MS increased respectively from 33.8 ± 3.6 to 52.4 ± 6.4 ng/g ($p < 0.01$) and 2.07 ± 0.06 to 2.62 ± 0.14 ng/g ($p < 0.01$) in the liver, and from 8.6 ± 1.1 to 17.9 ± 3.3 ng/g ($p < 0.01$) and 1.8 ± 0.1 to 2.7 ± 0.4 ng/g ($p < 0.01$) in the pancreas. In both tissues, PPC provided total protection against this oxidative stress, with restoration of 4-HNE and F_2-IP to normal. Alcohol decreased hepatic as well as pancreatic glutathione (GSH), whereas that of the liver was significantly increased by PPC. The mechanism of the protection has not been elucidated but does not involve vitamin E, which remained normal in both tissues. PPC most likely acts by boosting the cellular defense systems against the oxidative stress. Therefore, we found that PC species provided as PPC (such as 18:2 – 18:2 PC and 18:1 – 18:2 PC) are actively incorporated into liver phospholipids, and even more in those of pancreas. PPC supplementation restores the level of some PC species depleted by alcohol, and corrects the concomitant oxidative stress as well as GSH reduction in the liver and pancreas. We believe, that PPC should also be assessed for its beneficial effect in patients with pancreatic disorders.

Mechanisms for the Gender Difference in Ethanol's First-Pass Metabolism. C.S. Abittan[1,2], E. Baraona[1,2], M. Moretti[3], G. Pozzato[3], Z.W. Chayes[1], C. Schaefer[1], and C.S. Lieber[1,2]. [1]Section of Liver Disease and Nutrition, Alcohol Research Center, Bronx VA Medical Center, Bronx, NY; [2]Mount Sinai School of Medicine, New York, NY; and [3]University of Trieste, Trieste, Italy.

Blood alcohol levels are significantly lower after oral (PO) than intravenous (IV) ethanol, so-called first-pass metabolism (FPM). The responsible mechanism is still being debated, especially the respective roles of gastric emptying and metabolism, as well as the corresponding enzymes involved. To address these issues, 20 healthy volunteers (10 men and 10 women) were given PO ethanol (0.3 gm/kg of body wt) at various concentrations one hour after a standard meal. All women underwent a urine test to exclude pregnancy. FPM is traditionally assessed by the difference between the areas under the PO and the IV blood alcohol curves (AUC). In addition, we now use a more quantitative method, namely the integration of the Michaelis-Menten equation over the entire curve of blood alcohol concentrations. Gastric emptying was assessed with a nuclear scan performed on 8 men and 8 women using technetium-labeled diethylene triamine pentacetic acid (Tc^{99m}-DTPA). Each subject was given 10% ethanol (0.3 gm/kg of body wt) mixed with 300 µCurie of Tc^{99m} one hour after a standard meal. Blood alcohol concentrations were assessed using an alcohol breathalyzer every 5 minutes, starting at 15 minutes after consumption of ethanol and ending when the subjects' blood alcohol levels became undetectable. Activity of the various alcohol dehydrogenase (ADH) isozymes were quantified in gastric biopsies, using preferred substrates: acetaldehyde for Class I (gamma); m-nitrobenzaldehyde for Class IV (sigma); and glutathione-dependent formaldehyde dehydrogenase, a specific reaction of Class III (chi). A significantly lower FPM was confirmed in women by both the AUC and the integration methods. However, this could not be explained by a difference in gastric emptying. In fact, there was slower emptying in women than in men, which should favor an increased FPM. There was also no difference in gamma and sigma-ADH activities. By contrast, chi-ADH activity was significantly lower in women. The involvement of chi-ADH was then verified taking advantage of its unusual concentration dependency by comparing FPM at imbibed ethanol concentrations of 5% and 40%. Whereas there was no gender difference at 5%, there was a significantly lower FPM in women at 40%, which again incriminated chi-ADH activity.

In conclusion, this study shows that the gender difference in gastric FPM is not due to a difference in the emptying of ethanol from the stomach, but appears to be caused by a lower gastric metabolism of ethanol in females due to a significantly lesser activity of chi-ADH. The resulting higher blood alcohol levels may promote the greater vulnerability of women to the pharmacologic effects of ethanol and to the medical complications of alcoholism.

Cardiology

* **Conditional Lineage Ablation to Model Human Diseases.** A. Fischer[1], P. Lee[1], G. Morley[2], S. Factor[3], D. Vaidya[2], J. Jalife[2], and G.I. Fishman[1]. [1]Cardiovascular Institute, Section of Myocardial Biology, Mount Sinai School of Medicine, New York, NY; [2]Department of Pharmacology, [2]State University of New York, Syracuse, NY; and [3]Department of Pathology, Albert Einstein College of Medicine, Bronx, NY.

Apoprotein B100 Degradation and its Relationship to Protein Translocation and Hepatic Lipoprotein Assembly. R. Pariyarath, X. Wu, and E.A. Fisher. Department of Medicine, and Laboratory of Lipoprotein Research, Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Apoprotein B (apoB) is the major protein component of the atherogenic lipoproteins, very low density lipoprotein (VLDL) and low density lipoprotein (LDL). Unlike most hepatic proteins, the net secretion of apoB is regulated by intracellular degradation. A model system to study hepatic apoB degradation is the human hepatocarcinoma HepG2. When lipid synthesis is limited in HepG2 cells, apoB degradation by the ubiquitin/proteasome pathway is rapid and modulated by interaction of apoB with chaperones in the cytosol and the endoplasmic reticulum (ER). In recent studies, we have further investigated the topology of apoB during its translocation and assembly into lipoprotein particles. HepG2 cells were pre-treated with proteasomal inhibitor MG132 and labeled with 35S-methionine for 15 min. During a 60 min chase period (also containing MG132), cells were permeabilized and treated with the cross-linking agent, DSP. Treated lysates were then sequentially immunoprecipitated, first with anti-sec61β (sec61b, a translocon protein), then with anti-apoB. In the absence of oleic acid (-OA), apoB that was cross-linked to sec61β (apoB/sec61b) was readily detected by sulfate-polyacylamide gel electrophoresis (SDS-PAGE) throughout the chase period. When lipid synthesis was stimulated (+OA), apoB/sec61b was comparable up to 40 min to that in -OA. In contrast, at 60 min apoB/sec61b in +OA was reduced by 90% compared to -OA, signifying completion of translocation concomitant with the formation of a lipoprotein particle. Since the ER residence time of apoB is ~ 40 min, the data imply that apoB is associated with the translocon during lipoprotein assembly. Inhibition of microsomal triglyceride transfer protein (MTP) activity at the start of chase totally blocked apoB secretion +/-OA. However, if MTP was inhibited after 60 min of chase, there was no effect on lipidation and secretion of apoB +/-OA.

Conclusions: In HepG2, (1) nascent apoB has a prolonged interaction with the translocon during which it can be accessed by both the proteasome and lipoprotein assembly pathways; (2) apoB lipidation most likely occurs during this interaction; and (3) MTP activity is only necessary for early translocation and lipidation events.

^{201}Thallium SPECT Scintigraphy-Detected Apical Myocardial Ischemia as the Only Independent Territorial Determinant of Positivity of the Exercise ECG. P. Knez[1], S. Akbar[1], J.H. Tunio[1], C. Tziros[1], N. Solanki[1], A. Sutanda[1], A. Kamenetsky[1], L. Medepalli[1], and J.E. Madias[1,2]. [1]Department of Cardiology, Elmhurst Hospital Center, Elmhurst, NY; and [2]Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Ischemic changes in the exercise electrocardiogram (ECG), when it is interpreted as positive (+ECG), involve leads 2, 3, aVF, and V_4V_6, with almost no exception. This invariable response suggests that the ECG does not provide information regarding the specific location of the ischemic myocardial territory, or that the positivity of the ECG depends on the presence of exercise-induced transient ischemia in one or more regions, which, by virtue of their location, are particularly sensitive to the ischemia-detecting "scanning" of the ECG recording system. The above implies that certain myocardial territories, when ischemic, may not be associated with a +ECG, thus rendering a falsely negative ECG result. To investigate this, we employed percent count densities (%) from the ^{201}Thallium single proton emission computed tomography (SPECT) myocardial perfusion scintigraphic polar maps of the post-exercise images, utilizing a 4-compartment model (anterior {A}, posterior {P}, septal {S}, and lateral {L}), and a 5-compartment model including a truncated portion of the areas of the 4-compartment model (Aa, Pa, Sa, and La), plus apex (Ap), as indices of relative myocardial perfusion, in comparison with the best perfused area of the heart. Also an index of total ischemic burden (T) as T = A + P + S + L was employed. The ^{201}Thallium SPECT images corresponding to the exercise ECGs (+ECG or negative {-ECG}) were treated as a binary dependent variable, and the myocardial territories, described above, as the independent variables in a logistic regression analysis (Log. Reg.). Results, in % counts (x ± SD), of Log. Reg., and of univariate analysis (Univ.) were:

Variable	-ECG (n = 146)	+ECG (n = 60)	P (Univ.)	P (Log. Reg.)
Ap	68.8 ± 7.5	60.9 ± 10.7	0.0005	0.006
A	79.0 ± 5.5	75.3 ± 9.8	0.007	0.555
P	68.0 ± 7.8	62.4 ± 7.9	0.0005	0.572
S	71.2 ± 7.2	66.9 ± 10.8	0.006	0.213
L	80.2 ± 5.3	74.6 ± 8.3	0.0005	0.734
Aa	85.5 ± 6.1	83.1 ± 9.3	0.072	0.587
Pa	70.3 ± 8.7	65.8 ± 9.3	0.001	0.824
Sa	75.5 ± 7.4	72.8 ± 10.9	0.076	0.723
La	86.5 ± 5.6	81.7 ± 10.0	0.001	0.734
T	298.7 ± 18.9	277.8 ± 27.5	0.0005	0.321

Thus, presence or absence of myocardial ischemia of the territory of the Ap is the only independent regional determinant of the positivity or negativity of the exercise ECG, correspondingly. The mechanism by which the Ap exerts such an influence on the ECG may be its proximity to the chest wall, and/or its orientation to the electrode positions exercise ECG recording system.

A Direct Comparison of Metoprolol and Carvedilol in Congestive Heart Failure. M.L. Kukin, J. Kalman, D.K. Levy, C. Buchholz-Varley, O.N. Ocampo, and M. Steinmetz. The Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Carvedilol (C) is a novel β–blocker which blocks β–1, β–2 and α receptors and also has antioxidant properties. Metoprolol (M) is highly β–1 selective and has been extensively studied in congestive heart failure (CHF). To date, there have been no direct comparisons of these two β–blockers in a CHF population. We randomly assigned 59 pts (open label) to M or C. Baseline (Base) evaluation included New York Heart Association (NYHA) class, systolic blood pressure (SBP), heart rate (HR), symptom score, quality of life (QOL) index, 6 min walk (feet), and mVO_2 (mL/kg/min). Beta-blocker was gradually titrated to a target dose of 25 mg bid (50 mg bid if wt ≥ 85 kg) for both C and M. Background therapy consisted of angiotensin-converting enzyme inhibitor (ACEI) (93%), digoxin and diuretics. There were 42 men and 17 women; 24 ischemic, 30 idiopathic, 5 valvular with NYHA class II/ III/ IV: 12/41/6. Of the 59 pts (mean age 57, mean EF 18%), 48 completed 4 months of long-term therapy (LT). The entire group © and M) showed significant improvements ($p < 0.05$) in both the 2 clinical and 2 exercise parameters (analysis of variance [ANOVA] and paired T tests).

	SBP	HR	Symp	QOL	Walk	mVO_2
C - Base	107	87	11	50	1105	11
C - LT	107	70*#	8	40*	1182	12
M - Base	107	84	10	51	1239	11
M - LT	109	74*	9*	45	1356*	12*

(* = $p < 0.05$ within grp., # = $p < 0.05$ between grp.)

As seen in the table, both groups show parallel improvements over time in these clinical and exercise parameters. The only difference in response between C and M by ANOVA was in HR which may reflect a relatively larger dose of C than M and/or a specific effect of C on reducing coronary sinus norepinephrine. Thus, -blockers demonstrate significant benefits over 4 months in this CHF population with no discernible difference between C and M in the measured parameters.

Role of Cyclin-Dependent Kinase Inhibitor (CDKI) $p27^{KIP1}$ in Restenosis after Arterial Injury. M. Roqué[1], C. Cordón-Cardó[2], V. Fuster[1], and J.J. Badimón[1]. [1]Cardiovascular Institute, Mount Sinai School of Medicine and [2]Memorial Sloan-Kettering Center, New York, NY.

Smooth muscle cell proliferation is one of the major contributors to restenosis post-percutaneous transluminal coronary angioplasty (PTCA). Cell division is controlled by a series of positive and negative regulators at sequential points throughout the cell cycle. We previously reported the inhibitory effects of rapamycin on neointima formation post-PTCA in a porcine model. Rapamycin, an immunosuppressant macrolide, increases the expression of $p27^{kip1}$, a cyclin-dependent kinase (cdk) inhibitor, leading to inhibition of Rb phosphorylation and cell cycle arrest in G_1.

Aim: To study the time-course expression and localization of $p27^{kip1}$ in the vessel wall after PTCA.

Methods: Expression of p27 was assessed by immunohistochemistry in porcine coronary specimens (n = 65), harvested from 1 hour to 4 weeks after PTCA. An additional group of 18 coronaries from rapamycin-treated animals was also analyzed. Rapamycin was administered for 2 weeks after PTCA, and the coronaries harvested at 4 weeks post-intervention.

Results: One week after PTCA, the expression of p27 can already be identified in the adventitia. At 2 weeks, it is also present in the native media in 50% of the specimens, and at 4 weeks p27 expression is present in all specimens in the adventitia, native media and 30% in the endothelium. P27 expression is completely absent in the neointima throughout the restenotic process. Rapamycin treatment induced an increase in staining intensity for p27 in the adventitia, media and also in the neointima.

	Adventitia	Media	Neointima	Endothelium
week 1	+	-	-	-
week 2	+	±	-	±
week 3	+	+	-	+
Rapamycin	+++	+++	+	+

Conclusions: Expression of p27 in the arterial wall correlates with cell proliferation in the different components of the arterial wall. The inhibitory effects of rapamycin on restenosis post-PTCA seem to be mediated through overexpression of p27. This data suggest that new approaches targeting cell-cycle regulators may have potential therapeutic implications in the prevention of restenosis.

Antithrombotic Effect of ZD-2486, an Orally Active IIb/IIIa Receptor Antagonist. M. Roqué, J. Osende, S. Worthley, G. Helft, E. Acampado, J.H. Chesebro, V. Fuster, and J. J. Badimon. Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Platelet activation and thrombosis play a key role in the onset of acute coronary events. Glycoprotein (GP) IIb/IIIa receptor complex is the final modulator of platelet aggregation and thrombosis. Several clinical trials have demonstrated the beneficial effects of these agents and have suggested the need for long-term treatment, triggering the development of orally active agents.

We compared the effects of ZD-2486, Zeneca (Macclesfield, Cheshire, UK), an agent that mimics the RGD tripeptide sequence, versus heparin in a canine model. ZD-2486 is active following IV or oral administration. Thrombus formation was analyzed by deposition of autologous ^{111}In-platelets (PD) and ^{123}I-fibrinogen (FgD) in the Badimon perfusion chamber after 5-minute perfusions at low and high shear rate conditions (LSR, HSR). Dog tunica media served as thrombogenic substrate. The study included an initial IV dose-response followed by one-week treatment using the optimal antithrombotic dose selected from the IV study. No bleeding or thrombocytopenia was observed. Hematological parameters, activated partial thromboplastin time (aPTT), bleeding time and *in vitro* platelet aggregation were monitored.

Results: Platelet aggregation induced by adenosine diphosphate (ADP) and collagen was completely blocked. No prolongation of the aPTT was induced.

	HSR		LSR	
TREATMENT	PD (10^6/cm^2)	FgD (10^{12}/cm^2)	PD (10^6/cm^2)	FgD (10^{12}/cm^2)
UFH 100	214 ± 21	626 ± 63	24 ± 3	182 ± 23
ZD 0.3 mg/kg	274 ± 26	340 ± 32	25 ± 3	118 ± 12
ZD 0.4 mg/kg	187 ± 25	219 ± 33	11 ± 1*	107 ± 8
ZD 0.5 mg/kg	98 ± 14*	136 ± 18*	22 ± 3*	136 ± 18
ZD 1 mg/kg IV	36 ± 8*	103 ± 7*	11 ± 1*	85 ± 4*
ZD 1 mg/kg PO	26 ± 8*	244 ± 38*	17 ± 4*	180 ± 13

Conclusion: ZD 2486 reduced thrombus formation at both LSR and HSR conditions following IV or oral administration. The antithrombotic effect is more marked at HSR. Therefore, ZD-2486 seems to be a promising therapeutic agent to prevent thrombosis in conditions characterized by deep arterial injury.

Power Harmonics Imaging is Quantitatively Superior to Harmonic and Triggered Imaging for Contrast Myocardial Perfusion Imaging. T. Nahar, L. Croft, S. Buckley, O. David, E. Stern, G. Venkataraman, E. Fisher, and M.E. Goldman. The Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Contrast (C) echo may facilitate myocardial perfusion imaging (MPI). Different modalities have been advocated to image MPI by C: harmonic (H), power Doppler or power harmonic imaging (PHI, ATL, Bothell, WA) and ECG triggered (T).

Methods: To compare these methods we studied 14 subjects (4 males, 10 females, age = 41.7 ± 4.6 yr) all at very low risk for coronary disease, at baseline (B) and following multiple bolus injections of Optison™ (MBI, San Diego, CA; and Mallinckrodt, St. Louis, MO), a new albumin microsphere contrast agent containing octafluropropane with fundamental (F), H, PHI + T imaging using ATL HDI 5000CV. Digitized videodensity (VD) was measured (Nova-Microsonics) in 51 cm^2 regions {background as control, mid-LV cavity (CAV), basal LV septum (SEP), apex and basal lateral (LAT) walls} and quantified from 0 (black) to 100 (white). For 100 observations, the interobserver correlation was 0.99.

Results: All imaging modes increased myocardial VD with C compared to baseline ($p < 0.001$). But only PHI with C had significantly higher VD than all other modes with C for LV SEP, Apex and LAT walls (*$p < 0.0002$). The LV cavity was equally enhanced by the advanced modes. Thus, PHI may be the imaging mode of choice to evaluate myocardial perfusion with Optison™ echo contrast.

	B-F	C	B-H	H+C	B-PHI	PHI+C	B-T	T+C
SEP	41	52	41	60	53	82*	46	68
Apex	33	36	42	56	54	74*	46	63
LAT	23	31	24	30	32	56*	19	36
CAV	15	65	15	92	20	98*	17	93

Impact of Type of Health Insurance on Time for Evaluation in an Emergency Chest Pain Evaluation Unit of an Urban Academic Medical Center. I.K. Maher, M.E. Farkouh, B.J. Richardson, M. Henzlova, M. Sanders, and J.H. Chesebro. Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Objective: We determined the influence that type of health insurance may have on time to discharge from a chest pain unit for patients at intermediate risk for cardiac events by Agency for Health Care Policy and Research (AHCPR) guidelines. We recommend that all our intermediate risk patients be observed in a Chest Pain Evaluation Unit (CPEU).

Methods: We prospectively evaluated 147 patients seen at the Emergency Department of a large New York City academic medical center which fulfilled the AHCPR definition of unstable angina. Patients were classified as High, Intermediate, or Low Risk by AHCPR guidelines, which were instituted here in June 1996. At the time of risk stratification, both the time at triage and type of primary health insurance coverage were recorded. The health insurance status was categorized into three groups: Medicare, Medicaid and Private Insurance or Private Pay. The time from triage until discharge following observation and/or functional study was correlated with the patient's type of primary health insurance.

Results: The cohort was 50% male, 23% African-American, 46% Caucasian and 31% Hispanic. Of this group, 38 (25.9%) had Medicaid, 58 (39.5%) had Medicare, and 51 (34.7%) had Private Insurance or Private Pay. As classified by the AHCPR guideline, 11 (7.5%) of patients were High Risk, 87 (59.2%) Intermediate Risk and 49 (33.3%) Low Risk. Only 31 (35.6%) Intermediate Risk patents were further evaluated in the CPEU. Of those patients evaluated in the CPEU and who underwent observation and/or functional study: 9 patients had Medicaid (mean time to discharge = 44 hours), 12 patients had Medicare (mean time to discharge = 27 hours), and 6 patients had Private Insurance or Private Pay (mean time to discharge = 19 hours with a $p < 0.05$ for comparison of Medicaid/Medicare vs Private).

Conclusion: Patients with Private Insurance-Private Pay were evaluated and discharged from the chest pain unit in approximately 1/2 the time as compared to those with Medicaid or Medicare, respectively. Thus, a patient's health insurance may play a role in the timely performance of necessary testing and treatments and may be a factor in their overall quality of care. Our data also suggests that the CPEU is underutilized with only 1/3 of eligible patients being systematically evaluated.

Risk Stratification According to AHCPR Guidelines for Unstable Angina Reduces Hospital Admission in an Urban Academic Medical Center. I.K. Maher, M.E. Farkouh, B. Richardson, M. Sanders, M. Henzlova, and J.H. Chesebro. Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

To determine the influence of clinical practice guidelines for unstable angina on triage decisions by physicians in the Emergency Department, we prospectively evaluated 147 patients seen at the Emergency Department of a large New York City academic medical center. Previously, it was shown in a Midwest community cohort that Agency for Health Care Policy and Research (AHCPR) guideline appeared valid. Patients were classified as high, intermediate, or low risk according to the AHCPR guideline for unstable angina, which was originally instituted in our hospital on June 1996. We observed whether emergency physician's management were influenced by our adaptation of the guideline: High-Risk patients to be admitted, Intermediate-Risk patients to be evaluated in the Chest Pain Observation Unit within the Emergency Room, and Low-Risk patients to be discharge to the home.

This cohort was 50% male, 23% African-American, 46% Caucasian, and 31% Hispanic. Eleven (7.5%) were High Risk, 87 (59%) were Intermediate Risk, and 49 (33%) were Low Risk. All 11 High-Risk patients were admitted, whereas 36 (41%) of the Intermediate-Risk patients were directly admitted to an inpatient ward and 20 (23%) were sent directly home without further evaluation. Of 31 (36%) Intermediate-Risk patients further evaluated in the Chest Pain Observation Unit, 4 (13%) patients were eventually admitted to an inpatient ward or cardiac catheterization and 27 (87%) were sent home. Furthermore, 16 (52%) of Intermediate-Risk patients underwent a functional study of which 16 (100%) were discharged safely. Finally, 42 (86%) Low-Risk patients were discharged directly home whereas, 4 (8%) of Low-Risk patients were observed in the chest pain unit (CPU), and 3 (6%) of Low-Risk patients were admitted to inpatient wards. The 30-day and 6-month follow-ups are in progress.

Prior to our institution of the AHCPR guidelines, all intermediate risk patients were admitted to the hospital. Thus, we document a 30% decrease in admissions utilizing a CPU intervention.

Severe Coronary Artery Disease in Patients with Normal or Near Normal Myocardial Perfusion Stress Imaging. J.A. Diamond, D.A. Sandler, J. Machac, and M.J. Henzlova. Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

It is accepted that normal or near normal myocardial perfusion stress imaging with Tl-201 or Tc99m-Sestamibi suggests the absence of life-threatening coronary artery disease (CAD). We reviewed myocardial perfusion studies from the past 5 yrs in order to (1) define the proportion of false negative results, and (2) ascertain the features which may prevent misdiagnosis. Out of 9171 tests, 3992 (44%) were interpreted as normal or near normal; 97 (1%) patients subsequently (within 6 months) underwent coronary angiography. Seventy (22M/48F; 58 ± 13 yrs) had no significant CAD. Eight (5M/3F; 65 ± 8 yrs) had either left main (n = 3), severe proximal left anterior descending (LAD) (n = 3) or 3 vessel CAD (n = 2).

	No CAD n = 70	Severe CAD n = 8
Exercise/pharmacologic (pts)	43/27	5/3
Tl-201/Tc99m-Sestamibi (pts)	59/11	4/4
Artifacts (soft tissue attenuation, "hot spots") (pts)	24	5
Markers of severe CAD* (pts)	25	7**

* ↑lung uptake and/or transient cavity dilatation with Tl-201. ST-segment depression, chest pain and or hypotension with exercise.

* *p < 0.01 No CAD vs Severe CAD, 2-tail Fisher's Exact Test, Positive Predictor Value (PPV)= 7/32 (22%).

The peak heart rates achieved (exercise studies) were 89% and 87%, respectively. Although both groups had similar proportion of artifacts, patients with severe CAD had significantly more markers of severe CAD (p < 0.01). Thus, the referring physician should be aware of the possibility of significant CAD in patients having normal or near normal perfusion stress imaging accompanied by known markers of severe CAD.

Murine Model of Intimal Hyperplasia: Femoral Artery Endovascular Injury. E.D. Reis[1], M. Roque[2], J.T. Fallon[2], W.X. Zhang[1], H. Weinberg[1], J.J. Badimon[2], M.B. Taubman[2], and L.H. Hollier[1]. Departments of [1]Surgery and [2]Medicine, Mount Sinai School of Medicine, New York, NY.

The development of intimal hyperplasia (IH) following arterial injury is one of the most investigated problems in cardiovascular disease—often described but still poorly understood. Genetically-modified mice can be used to study endogenous molecules regulating IH. However, to date there has been no reliable way to effectively induce intimal injury and IH in the mouse. We developed a new method of endovascular injury and evaluated IH in C57 and FVB mice, 2 strains commonly used for the generation of transgenic mice.

Methods: Thirty-nine male and female mice of the C57BL/6 and FVB strains, 4–6 months old, were studied. The common femoral artery was injured by passage of a modified endodontic broach through an incision in the superficial femoral artery. Two weeks after injury, arterial segments were harvested for histological and morphometrical analysis.

Results: Operative mortality was 5%. Occlusive thrombus was found in 11 arteries, 3 in the C57 and 8 in the FVB group. Severe damage of the arterial wall with necrosis was found in 3 arteries. Two arteries appeared uninjured and had no IH. The remainder arteries (n = 21) had IH. The table summarizes the morphometric data of this latter group (mean ± SEM):

	C57BL/6		FVB	
Gender	M (n = 6)	F (n = 4)	M (n = 5)	F (n = 6)
% Stenosis	27±7	42±8	23±4	22±5
Intimal Area (mm²)	13,036±3,256	17.789±3,266	18,941±3,755	13,211±2,190
Intima/Media ratio	0.9±02	1.1±0.2	1.2±0.2	0.9±0.1

Statistical analysis showed no significant strain- or gender-related differences in terms of degree of stenosis and intimal formation.

Conclusions: This method of arterial endovascular injury induces IH in C57BL/6 and FVB mice. Our data suggest that the response-to-injury is similar for male and female mice of these two strains. This technique is suitable for use in mouse models of human cardiovascular disease to examine the molecular and genetic mechanisms of vascular pathobiology.

Rat Carotid Interposition Graft: A Useful Model for Vascular Biology. A. Shrivastava, W.X. Zhang, J.T. Fallon, H. Weinberg, and E.D. Reis. Vascular Microsurgery Laboratory, Mount Sinai School of Medicine, New York, NY.

Background: Both chronic and accelerated atherosclerosis result from an inflammatory-fibroproliferative response to injury to the arterial wall. This is due to activation of endothelial and smooth muscle cells by physical, immunological or hemodynamic factors. Arterial transplantation in rodents using microsurgical techniques can be useful to study the mechanisms regulating these processes and to test therapeutic strategies. In this preliminary study, a model of carotid interposition graft was developed in the rat, its feasibility assessed, and morphological changes in the graft studied over time.

Methods: Unilateral or bilateral autotransplantation of a segment of the common carotid artery was performed in the rat. Through a midline neck incision, the common carotid artery was isolated, occluded proximally and distally, and a 5–9-mm segment was excised and re-implanted *in situ*. In bilateral experiments, one side had the segment inserted in reverse direction (arterial reversal graft). The anastomoses were performed with sutures of 11-0 nylon monofilament under 10–15x magnification. Vessels were harvested at 1, 2, 4 and 8 weeks and processed for histology.

Results: The mean operative time was 30 min/graft. The operative mortality was 0%. Occlusive thrombus was found in 10% arteries (5% reversed and 5% non-reversed, patency rate 90%). Severe damage of the arterial wall with necrosis was found in 5% arteries, reflecting surgical trauma. No significant intimal hyperplasia was observed during the 2-month period of follow-up.

Conclusions: The present model of microsurgical arterial grafting is highly feasible and reproducible. As the rat is a well-characterized species for vascular and transplantation research, the applicability and utility of the carotid interposition graft are enormous. In particular, the unique utility of the carotid model lies in its parallelism or bilaterality—each experimental vessel having a (contralateral) 'built-in' control vessel. This model, thus, would be an extremely useful and practical vehicle for the demonstration of the effects of such interventions as gene therapy, drug therapy, immunologic manipulation, or allogeneic/syngeneic transplant of arteries, having the experiment and control "side-by-side" in the same animal. In the present study, we examined the outcome of reversed arterial interposition. No significant effect in terms of intimal thickening was observed at two months.

The carotid artery is widely used for vascular injury experiments. It also has adequate diameter for creation of microsurgical anastomoses. The carotid system may be a higher flow system compared to the femoral arteries. This, combined with the lack of branches and parallel position in the neck, are potential advantages of the proposed model.

The carotid interposition graft has multiple applications in research, as endothelial effects (in this preliminary study, direction-specific), such as receptor activation (and resultant smooth muscle cell proliferation/intimal thickening) represent useful targets for therapeutic interventions such as drug, antibody or gene therapy (via *in vitro* vessel manipulation, or *in vivo*). In addition, this model can be used as an alternative for arterial transplantation experiments.

Coronary Angiographic Findings in Patients Who Sustained Acute MI and Received TPA. A. Ababneh, and J.I. Haft. Department of Cardiology, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Background: Thrombolysin in myocardial infarction (TIMI3) flow has been considered the goal of tissue plasminogen activator (TPA) therapy. However, in patients with stable coronary disease almost all lesions including 98%+ lesions exhibit TIMI3 flow at coronary angiography. In studies of TPA effect, the residual luminal narrowing after TPA is rarely discussed.

Methods: To determine the lesion severity in patients after TPA, 97 patients who presented with evidence of acute myocardial infarction (MI) (ST elevation), who received TPA and then underwent coronary angiography within 3–7 days, were reviewed.

Results:

I. Culprit artery total occlusion was seen in 15 patients (15%), 13 had < 70% lesions (13%), 19 had 70–90% lesions (20%) and 50 had 90–99% lesions (52%). TIMI3 flow occurred in 80 of 82 with patent vessels (only 2 patients had TIMI2 flow). Morphological angiographic evidence of ruptured plaque was present in 72 of the 82 patients without total occlusion (88%). On the basis of cath findings, 64 went on to percutaneous transluminal coronary angioplasty (PTCA), 14 had coronary artery bypass graft (CABG), and 19 were treated medically.

II. In a subgroup of 52 of the 97 patients who did not have post-MI clinical evidence of ischemia (no spontaneous angina), had no stress test, and were catheterized routinely 3–7 days after MI, findings were similar: 6 (11%) had < 70% lesions, 9 (17%) had 70–99% lesions, 27 (52%) had 90–99% lesions and 10 (19%) had total occlusions. Ruptured plaque was seen in 37/42 (88%) of these patients.

Conclusions: Although almost all patients after TPA have TIMI3 flow (3–7 days and after receiving the standard MI therapy), almost 84% (69/82) have lesions >70%. Ruptured plaque is evidence in 88% of lesions. These findings suggest that TPA may save lives and prevent or minimize MI, but severe residual lesions are the rule. Although early studies (TIMI2B, SWIF) have suggested that not all patients require catheterization after TPA, with newer more effective and safer therapeutic technology available, routine catheterization should be considered.

Reduction of Transient Outward Currents Induces Heart Failure in Transgenic Mice. P. Lee, A. Wickeder, P.H. Backx, and G.I. Fishman. Cardiovascular Institute, Section of Myocardial Biology, Mount Sinai School of Medicine, New York, NY; and Departments of Medicine and Physiology, University of Toronto, Canada.

Anisotropy May Create Echo Myocardial Perfusion 'Pseudo-defects.' A.E. Schussheim, L.B. Croft, T. Nahar, S. Buckley, C. Soltero, O. David, and M.E. Goldman. The Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Depressed Midwall Fractional Shortening Predicts Diastolic Dysfunction in Asymptomatic Hypertensive Patients. A.E. Schussheim, J.A. Diamond, J.S. Jhang, and R.A. Phillips. Hypertension Division, The Zena and Michael A. Weiner Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Inducible Knock-Out System for the Connexin43 Gap Junction Channel Gene. D.E. Gutstein, M. Srinivas, and G.I. Fishman. Cardiovascular Institute, Section of Myocardial Biology, Mount Sinai School of Medicine, New York, NY.

Is Ibutilide a Negative Inotrope for the Left Atrial Appendage? L. Baruch, and J. Banker. Bronx Va Medical Center, Bronx, NY, and Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Can Transesophageal Echocardiography Predict Successful Cardioversion of Atrial Arrhythmias with Ibutilide? J. Banker, and L. Baruch. Bronx VA Medical Center, Bronx, NY, and Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Is Blunted Pulmonary Venous Flow a Marker of Poor Prognosis in Patients with Congestive Heart Failure? M. Pu, X. Fan, S. Guerra, P.G. Patacsil, A. Hameed, C. Eng, and L. Baruch, Bronx VA Medical Center, Bronx, NY and Mount Sinai School of Medicine, New York, NY.

Sorcin Associates with the Pore-forming Subunit of Voltage-Dependent L-type Ca^{2+} Channels. M. Meyers[1], T.S. Puri[2], A.J. Chien[2], T. Gao[2], P-H Hsu[1], M.M. Hosey[2], and G.I. Fishman[1]. [1]Cardiovascular Institute, Section of Myocardial Biology, Mount Sinai School of Medicine, New York, NY; and [2]Departments of Molecular Pharmacology and Biological Chemistry, Northwestern University, Chicago, IL.

Clinical Geriatrics

Primary Prevention of Osteoporosis in the Ambulatory Clinic of a Community Hospital. N. Logvinenko, and M. Patero Schori. Department of Medicine, Englewood Hospital and Medical Center, Englewood, NJ.

Background: In spite of the well-known benefits of primary prevention of osteoporosis, prevention methods are not adequate despite the tremendous financial and emotional cost of osteoporotic fractures which cannot compare with the easy and inexpensive preventive methods available.

Objective: We decided to determine the adequacy of primary prevention of osteoporosis in the outpatient clinic of a community hospital in Northern New Jersey.

Design: A retrospective review of charts of medical clinic patients.

Setting: An outpatient clinic in a community Hospital in Northern New Jersey.

Participants: Postmenopausal women over the age of 50 years.

Results: Among 150 postmenopausal women over the age of 50 years, 55% received some form of prevention for osteoporosis. Of these: 10% received Hormonal Replacement Therapy (HRT), 21% - HRT with Ca and Vit D, 62% - Ca with Vit D, 6% - only Ca. Forty-five percent did not receive any form of primary prevention; 31% of them had contraindications to HRT; only 1 patient had contraindications to Ca; and 63% of patients not receiving prophylaxis were never offered anything.

Conclusion: As in other outpatient settings, the primary prevention of osteoporosis in our clinic is significantly underprescribed. It is due mostly to inadequate information given to the patients based on the review of charts of women. There is great potential for improving utilization of primary prevention of osteoporosis in the clinic and potentially significantly reduction of the risk of osteoporotic fractures.

The Association of Tamoxifen with Independence in ADLs and with the Prevalence of Alzheimer's Disease in Nursing Home Residents. B. Breuer[1]; S. Wallenstein[2], and R. Anderson[2]. [1]ULCS The Jewish Home and Hospital; and [2]Department of Biomathematics, Mount Sinai School of Medicine, New York, NY.

Evidence about the protective effect of estrogen against Alzheimer's Disease is equivocal. As tamoxifen (TAM) sometimes acts as an estrogen antagonist and at other times as an estrogen agonist, we investigated the association of this drug with the prevalence of Alzheimer's Disease (AD), as well as with independence in activities of daily living (ADLs). The data come from the 1993 New York State Minimum Data Set (MDS). Data analysis was limited to females over the age of 65 years. Tamoxifen treatment was documented for 1,385 of 93,031 women. For each woman receiving TAM, we chose up to 4 comparison women not receiving this drug. The women were matched on age, ethnicity, and nursing home. Analysis of the matched sets indicated that the prevalence of AD among women receiving TAM was 32.6% lower than women not receiving it ($p < 0.0001$). Similarly, the degree of independence in eating, toileting, and transferring was greater among women receiving this drug ($p \le 0.0004$). While the data suggest that TAM treatment preserves independence in ADLs and protects against Alzheimer's Disease, definitive conclusions may be drawn only from prospective clinical trials. Thus, it is fortuitous that there will soon be a clinical trial that will compare the effects of TAM and raloxifene treatments.

Drug Treatment of Hypertension in Elderly Patients. J. Ness, G. Mendelson, and W.S. Aronow. Department of Geriatrics, Mount Sinai School of Medicine, New York, NY.

A retrospective analysis of charts from all older patients (pts) seen from December 1, 1997–August 1, 1998 at an academic hospital-based geriatrics practice investigated the prevalence of different drugs used to treat hypertension (HT) after educational efforts. HT was diagnosed if the systolic blood pressure was greater than or equal to 140 mm Hg or the diastolic blood pressure was greater than or equal to 90 mm Hg. The study included 1,360 women and 459 men, mean age 80 +/- 8 years. HT occurred in 1,051 of 1,819 pts (58%). In a previous study, HT in 420 pts was treated with calcium channel blockers in 197 pts (47%), with angiotensin-converting enzyme (ACE) inhibitors in 160 pts (38%), with diuretics in 154 pts (37%), and with β-blockers in 55 pts (13%). In 121 pts with myocardial infarction, 54 (45%) were treated with calcium channel blockers and 23 (19%) with β-blockers. After educational efforts, of 1,051 pts with HT, 520 (49%) were treated with diuretics, 297 (28%) with β-blockers, 445 (42%) with ACE inhibitors, 171 (16%) with calcium channel blockers, 13 (1%) with other drugs, and 41 (4%) with no drugs. The last blood pressure recorded on the chart was less than 140/90 mm Hg in 735 of 1,051 pts (70%) with HT. Of 306 pts with HT and prior myocardial infarction, 182 (59%) were treated with β-blockers, 146 (48%) with ACE inhibitors, 96 (31%) with diuretics, and 29 (9%) with calcium channel blockers.

Conclusion: Educational efforts led to an increased use of diuretics and β-blockers, and a decreased use of calcium channel blockers in treating HT.

Ethnicity as a Factor Affecting Adjustment of Elderly to a Nursing Home. S. Sasson. Jewish Home and Hospital, Bronx, NY.

Predictors of Outcome at Discharge from Subacute Rehabilitation. A. Likourezos, M. Si, W. Kim, B. Breuer, J. Frank, S. Simmons, Z. Huang, and R. Neufeld. The Jewish Home and Hospital, and The Mount Sinai School of Medicine, New York, NY.

Clinical Immunology

Defect in Il-10 Mediated T Cell Dependent B Cell Differentiation in Common Variable Immunodeficiency (CVI). Y. Kuang, A. Harrington, X. Zheng, and L. Mayer. Division of Clinical Immunology, Mount Sinai School of Medicine, New York, NY.

Previous studies have reported a variety of cellular defects in patients with CVI. Many of these studies utilized artificial systems to induce immunoglobulin secretion. We have recently described a system whereby IL-10 can induce T cell-dependent immunoglobulin (Ig) secretion in normal human B cells. Interestingly, patients with CVI have normal to elevated levels of IL-10 yet fail to produce Ig *in vivo*. We therefore studied IgG secretion in T and B cell co-cultures from 15 CVI patients. Co-cultures of B and T cells in the presence of IL-10 (100 ng/mL) from all 10 normal healthy blood donors secreted IgG at high levels (14.0 ± 5.2 µg/mL, stimulation index (SI) = 28.1 ± 8.2), but the same co-cultures from CVI patients failed to yield detectable IgG (0.2 ± 0.1 µg/mL, SI = 1.2 ± 0.1). Similarly, IgM secretion was not noted. Since this system requires the functional integrity of both T and B cells, we performed studies designed to ascertain the nature of the defect in CVI patients. Normal allogeneic T and B cell co-cultures were established. In normal control cultures, allogeneic T cells were similarly capable of inducing normal B cells to secrete IgG in the presence of IL-10 (auto: 5.95 µg/mL; allo: 5.45 µg/mL). In 4/6 patients, B cells failed to secrete IgG in the presence of allogeneic normal T cells, but their T cells failed to induce IgG secretion by normal B cells as well. In the remaining 2 patients, normal T cells were capable of stimulating IgG secretion by CVI B cells, but at only 1/3 the level of the normal control. In this more physiologic system, the defects in CVI patients' immune function appear to reside in both T help and B cell maturation.

The Novel CD8 Ligand gp180 is a New Subfamily Member of the CEA Family of Glycoproteins. X.Y. Yio. Division of Clinical Immunology, Mount Sinai School of Medicine, New York, NY.

Previous studies have shown that the activation of CD8+ suppressor T cells by intestinal epithelial cells (IEC) appears to be mediated by both a novel IEC membrane glycoprotein, gp180, and the class Ib molecule CD1d. Amino acid sequence data have suggested that gp180 belongs to the family of carcinoembryonic antigen (CEA). The N-terminal sequence of gp180 exhibited high homology (83 – 100%) to CEA and nonspecific cross-reacting antigen (NCA) but internal sequences were distinct. We therefore analyzed the biochemical and functional differences between CEA and gp180. gp180 and CEA were purified from T84 cells on a mAb B9 (anti-gp180) and anti-CEA mAb affinity column, respectively. There was roughly 16-fold more CEA than gp180 in these cells. The purified proteins were subjected to V8 protease digestion. While the patterns were similar, there was an additional 18 kD band resolved in the CEA. Functionally, purified gp180 but not CEA was capable of binding to CD8 and activating CD8 associated p56lck in a CD8$/α$ cDNA transfectant. Further evidence for the distinct nature of these 2 molecules came from the DNA sequence. By reverse transcription polymerase chain reaction (RT-PCR) using specific primers derived from the distinct internal protein sequence of gp180, a 580 nucleotide clone, RT-2, was isolated and sequenced. The 5'-end of RT-2 was highly homologous to the 5'-end of CEA cDNA. From the 3'-end of RT-2, the first 52 nucleotides bore no homology to CEA. A gp180-specific probe resolved a 3.5 kb band by northern blot analysis. These results clearly demonstrate that gp180 is a uniquely functional novel member of the CEA family of glycoproteins.

Preferential Activation by IL-2 of a Truncated (Inhibitory) Isoform of Stat 5b in Splenic T Cells from Tumor-Bearing Mice. S. Salvadori[1], H. Sadowski[2], and K. Zier[1]. [1]Department of Medicine, Division of Clinical Immunology, and [2]Department of Biochemistry, Mount Sinai School of Medicine, New York, NY.

It has long been thought that the failure to reject a tumor can be a result of the inability of the immune system to generate a response to the tumor due to its poor antigen-presenting ability. However, evidence in several systems has revealed that an ongoing anti-tumor response can be downregulated even after it has been established. Thus, a significant problem in tumor rejection may actually be the active suppression of an appropriately generated response, rather than the inability of the host to respond at all. The development of functional responses by T cells depends upon signals transduced following the binding of ligand by the T cell receptor (TCR). The subsequent binding of Interleukin-2 (IL-2) results in the activation of Jak kinases, leading to the subsequent nuclear translocation of transcription factors, such as Stat 3 and Stat 5, where they bind specific DNA in the promoter, enabling the expression of target genes. The binding of IL-2 by its receptor leads to receptor aggregation and the activation of associated kinases, including $p56^{lck}$, Jak 1 and Jak 3, that in turn induce the activation of transcription factors such Stat 3 and Stat 5. Based upon our previous observation that IL-2-dependent responses, including the proliferation and the generation of CTL, were depressed in T cells from tumor-bearing mice, we postulated that defective signaling through the Jak/Stat pathway might interfere with the ability of the T cells to respond to IL-2. To test this hypothesis we studied the expression of Stat 5 in tumor-bearing mice. We observed that levels of Stat 5 were reduced in the cytosol of T cells from tumor-suppressed mice compared to controls. Subsequent experiments demonstrated that nuclear levels of Stat 5b in the nucleus were decreased even further. Most interestingly, however, we observed that tumor-suppressed mice had lost virtually all of the full-length form of phosphorylated Stat 5 and instead contained only a truncated form of the protein. While control mice also contained some truncated Stat 5, it was always expressed in the presence of abundant levels of the full-length protein. In contrast, tumor-bearing mice usually contained barely detectable levels of phosphorylated Stat 5 in the cytosol and in the nucleus only the truncated form. Subsequent experiments revealed that the truncated phospho-Stat 5 was able to bind DNA. This is important, since in myeloid cell lines truncated Stat 5 acts as a dominant negative to inhibit the expression of the Stat 5 target genes. Thus, while IL-2 signaling can occur in T cells of tumor-suppressed mice, they are less sensitive in terms of Stat 5 activation compared to tumor-immune mice and what is activated is the short form. These results suggest a molecular basis for non-responsiveness by T cells in tumor-bearing hosts.

CD8+ T Cells Are Pre-committed to Have Either a Suppressive or Cytolytic Phenotype. N.A. Campbell and L. Mayer. Division of Clinical Immunology, Mount Sinai School of Medicine, New York, NY.

Previous studies have shown that intestinal epithelial cells (IECs) are capable of selectively activating CD8+ suppressor T cells. This activation is mediated by a novel complex which is recognized by the T cell receptor (TCR):CD8 co-receptor complex on suppressor T cells and consists of the class Ib molecule CD1d and an associated epithelial cell surface glycoprotein, gp180. Since gp180 binds to any CD8 molecule, we wanted to determine whether IECs were targeting a selected subpopulation of pre-committed "pre-suppressor" cells or whether the CD1d:gp180 complex was transducing a specific signal that promoted suppressor cell generation from uncommitted CD8+ T cells. A 3-fold approach was taken: initially, the ability of IECs to activate CD28+ versus CD28- CD8+ T cells was determined; the signaling cascade in suppressor and cytolytic T cells was then compared; and the ability of gp180 to bind to the CD8 molecule and interfere with CTL effector function was investigated. IECs activate p56lck only in CD8+CD28- T cells and not in CD4+ or CD8+CD28+ T cells, although soluble gp180 is capable of activating p56lck in both CD8+ T cell subsets. This suggested that a selected subpopulation was involved. Both CD8+ T cells with suppressor and cytolytic activity were activated via the mitogen activated protein (MAP) kinase cascade. However, the activation of this MAP kinase pathway in IEC activated T cells was accomplished via the nucleotide exchange factor vav rather than the phospholipase C-gamma 1 (PLC-g1) pathway observed in cytotoxic lymphocyte (CTL). This suggests that these subsets of CD8+ T cells signal through distinct pathways.

In T cells activated by IECS, it was found that ZAP70 and vav were phosphorylated and recruited to z, p59fyn and p56lck. Finally, while soluble gp180 bound to CD8 on CTLs, it was not able to inhibit CTL killing when compared to anti-class I major histocompatibility complex (MHC) and anti-CD8 mAbs. These data suggest that the complex of CD1d and gp180 on IECs helps to target and signal a specific subpopulation of CD8+ T cells which may be functionally distinct from classical class I restricted CD8+ T cells.

The Non-Classical Class I Molecule Cd1d Associates with The Novel CD8 Ligand Gp180. N.A. Campbell[1], H.S. Kim[2], R.S. Blumberg[2], and L. Mayer[1]. [1]Division of Clinical Immunology, Mount Sinai School of Medicine, New York, NY, and [2]GI Department, Brigham and Women's Hospital, Boston, MA.

Previous studies have shown that normal intestinal epithelial cells (IECs) are able to selectively activate CD8+ suppressor T cells inducing proliferation associated with the activation of both the CD8-associated kinase p56lck and the T cell receptor (TCR)-associated kinase p59fyn. This process appears to relate in part to a 180 kd IEC surface glycoprotein, gp180, which binds to CD8 and activates CD8-associated p56lck. However, purified gp180 alone is unable to induce T cell proliferation and does not activate p59fyn. Since the class Ib molecule CD1d is expressed by IECs and mAbs against CD1d inhibit IEC-induced proliferation of CD8+ T cells, co-immunoprecipitation and ELISA studies were performed, and they demonstrated an association of gp180 and CD1d on the IEC surface.

Interestingly, the activation of p59fyn in IEC:T cell co-cultures was blocked by the anti-CD1d mAb D5 but not by the anti-gp180 mAb B9. Conversely, treatment of IECs with mAb B9 inhibited IEC-induced activation of p56lck but not p59fyn.

More directly, a human CD1d cDNA (FO-1 D5) transfectant was able to activate p59fyn but not p56lck. These data suggest that the CD1d:gp180 complex on the surface of IECs can be recognized by the TCR:CD8 co-receptor resulting in the activation of CD8+ T cells.

Dermatology

8-Methoxy-Psoralen and Ultraviolet A (PUVA) Induce the Formation of 8-hydroxy-2'-deoxyguanosine and DNA Fragments in Calf Thymus DNA and Human Epidermoid Carcinoma Cells. Z. Liu[1], Y. Lu[1], M. Lebwohl[1], and H. Wei [1,2]. Departments of [1]Dermatology and [2]Community Medicine, Mount Sinai School of Medicine, New York, NY.

The objective of this study is to investigate if 8-methoxy-psoralen (8-MOP) and ultraviolet A (UVA) radiation (PUVA) induce oxidative DNA damage. When calf thymus DNA was incubated with 8-MOP and irradiated with UVA (335 400 nm), the level of 8-hydroxy-2'-deoxyguanosine (8-OHdG) was substantially elevated by UVA. Formation of 8-OHdG correlated proportionally with both UV dose and 8-MOP concentration. Human epidermoid carcinoma cells were incubated_with 10 mg 8-MOP per mL, followed by 25 kJ/m^2 UVA. The level of 8-OHdG increased by nearly 3-fold in PUVA-treated cells compared to 8-MOP and UVA controls. To confirm what reactive oxygen species (ROS) are involved in PUVA-induced oxidative DNA damage, less or more specific ROS quenchers were added to DNA solution. The results showed that only sodium azide and genistein significantly quenched PUVA-induced 8-OHdG, whereas catalase, superoxide dismutase and mannitol exhibited no effect. Our studies suggest that PUVA induced the formation of 8-OHdG in purified DNA and cultured cells by UVA and that singlet oxygen is the principle oxidized species to oxidize DNA bases.

Chronic Exposure to UVB Increases the Levels of 8-hydroxy-2'-deoxyguanosine in Skin and Internal Organs of Hairless Mice. H. Wei, X. Zhang, Y. Wang, and M. Lebwohl. Department of Dermatology, Mount Sinai School of Medicine, New York, NY.

Oxidative DNA damage is known to play an important role in carcinogenesis and aging. We have investigated the effect of ultraviolet B (UVB) exposure on the formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG) in SKH hairless mice. Subacute exposure to low (3 kJ/m^2 x 6) and high (15 kJ/m^2 x 3) doses of UVB substantially increased the levels of 8-OHdG in mouse epidermis in a dose- and time-dependent fashion. However, the levels of 8-OHdG in internal organs remained unchanged. When mice were chronically exposed to UVB twice weekly at a dose of 0.9 kJ/m^2 for 20 weeks, significant induction of 8-OHdG was observed in both epidermis and internal organs such as brain, liver and spleen. However, there was no significant induction of 8-OHdG in mouse kidney. Topical application of isoflavone genistein, which substantially inhibits UVB-induced skin tumorigenesis, blocked UVB-induced 8-OHdG in both epidermis and internal organs. Our study suggests that chronic exposure to UVB not only induced oxidative DNA damage in the local tissues but also systemically affects vital internal organs. Therefore, the induction of oxidative DNA damage in local and internal organs may provide a novel mechanistic insight into photocarcinogenesis and immunosuppression.

Tamoxifen Inhibits Endogenous and UV Light-Induced Oxidative Damage to DNA, Lipids and Protein *In Vitro* and *In Vivo*. H. Wei, Q. Cai, L. Tian, and M. Lebwohl. Department of Dermatology, Mount Sinai School of Medicine, New York, NY.

We have investigated the effect of tamoxifen (TAM) on endogenous or ultraviolet radiation (UVR)-induced oxidative damage to macromolecules *in vitro* and *in vivo*. Both TAM and 4-hydroxytamoxifen (4-OH-TAM) inhibited UVR-induced formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG) in calf thymus DNA. Ascorbic acid exhibited a similar quenching effect as TAM, whereas glutathione had little effect on UVR-induced 8-OHdG. The order efficacy was: 4-OH-TAM > TAM » ascorbic acid > glutathione. The effects of TAM on endogenous 8-OHdG formation, lipid peroxidation and protein oxidation were examined SENCAR mice. Topical TAM significantly reduced the level of 8-OHdG in mouse epidermis by 27% ($p < 0.05$). Endogenous malondialdehyde (MDA) and carbonyl content were also substantially reduced by topical TAM. Furthermore, the effect of TAM on UVR-induced 8-OHdG and MDA in skin of hairless mice was evaluated. TAM significantly inhibited both 8-OHdG by 57 and 81%, and MDA by 37 and 65%, respectively, in mouse epidermis exposed to low (3 kJ/m^2 x 6) and high (15 kJ/m^2 x 3) doses of UVB irradiation. Our studies suggest that modulation of oxidative damages to macromolecules *in vivo* may explain at least in part the anticarcinogenic and chemopreventive actions of tamoxifen.

Synergistic Action of Benzo(a)pyrene and UVA Radiation on H_2O_2 Production and Oxidative DNA Damage in Human Epidermoid Carcinoma Cells. H. Wei, Z. Liu, Y. Lu, B. Rosenstein, and M. Lebwohl. Department of Dermatology, Mount Sinai School of Medicine, New York, NY.

The objective of this study is to investigate if benzo(a)pyrene (BaP) and ultraviolet radiation (UVR) synergistically induce H_2O_2 production and oxidative DNA damage. Calf thymus DNA was incubated with BaP and irradiated with UVB (280–320 nm) and UVA (335–400 nm). BaP substantially enhanced the formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG) by UVA, but only moderately increased the level of 8-OHdG by UVB. Human epidermoid carcinoma cells were incubated with 10 mg BaP for 24 hr and then exposed to 10 kJ/m^2 UVB and 25 kJ/m^2 UVA. UVB plus BaP did not affect the level of H_2O_2 and of 8-OHdG in cultured cells, whereas UVA plus BaP substantially increased H_2O_2 and 8-OHdG by over 10- and 4-fold compared to BaP and UVA controls. To confirm what reactive oxygen spacing (ROS) are involved in BaP plus UVR-induced oxidative DNA damage, less or more specific ROS quenchers were used. The results showed that only superoxidized dismutase (SOD) significantly quenched BaP plus UVA-induced 8-OHdG, whereas and NaN_3 and mannitol exhibited no effect. In contrast, catalase moderately increased the formation of 8-OHdG. Our studies show that UVA induces the formation of 8-OHdG in BaP-co-incubated DNA and cells more potently than UVB, and that $O_2^{\cdot-}$ plays an important role in synergistic induction of oxidative DNA damage.

Endocrinology

A New Graves' Disease Susceptibility Locus (GD-1) Maps to Chromosome 14q31. Y. Tomer[1], G. Barbesino[1], D.A. Greenberg[2], E. Concepcion[1], and T.F. Davies[1]. [1]Division of Endocrinology and Metabolism, Department of Medicine, and [2]Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

Epidemiologic data point to a genetic susceptibility to the autoimmune thyroid diseases (AITDs), including Graves' disease (GD) and Hashimoto's thyroiditis (HT); we have, therefore, initiated a whole genome search for the hypothesized susceptibility genes. Chromosome 14 contains at least 6 important candidate genes for AITDs, including the thyroid-stimulating hormone (TSH) receptor, multinodular goiter-1 (MNG-1), IgH, T cell receptor-α (TCR-A), estrogen receptor-β (ESR-B), and insulin-dependent diabetes mellitus (IDDM)-11 genes. Therefore, we have decided to screen chromosome 14 for possible loci linked with AITDs. In preliminary screening of 19 families, we identified a locus (GD-1) on chromosome 14q31 which was specifically linked to GD and not to HT (Y. Tomer et al, J Clin Endocrinol Metab 1997: 82:1645-1648). We have now screened chromosome 14 with a dense set of markers (1 – 10 cm apart) and a larger study sample. Additionally, specific candidate genes on chromosome 14 were examined individually (TSH-R, IgH, TCR-A, ESR-B, MNG-1, and IDDM-11). A total of 19 markers were used to screen chromosome 14, and their details are available from the genome data base (http://gdbwww.gdb.org/). Forty-eight multi-generational, families (308 individuals) were enrolled in the current study. Microsatellite markers were amplified using fluorescent labeled primers and genotyped using an ABI-310 genetic analyzer. Two-point and multipoint log of the odds (LOD) scores were calculated using the LIPED and GeneHunter programs, respectively. No linkage was observed with the combined AITD group (GD+HT), or HT only, for all of the chromosome 14 markers. However, positive LOD scores were obtained in the region of 14q31 when considering only GD patients as affected. The maximum LOD score was obtained for marker D14S81 (2.1, for the recessive model, at a penetrance of 0.3, and a recombination fraction of 0.01), thus confirming our earlier results. A multipoint analysis mapped GD-1 2 cM telomeric to D14S81 giving a multipoint LOD score of **2.7**. No linkage was observed with either GD, HT, or AITD for any of the candidate genes on chromosome 14. However, GD-1 was found to be located ~3 cM from the recently reported MNG-1 locus and ~13 cM from IDDM-11. GD-1 was located ~20 cM from the TSHR gene, and we found no evidence for linkage between markers inside the TSH-receptor gene and GD. In conclusion, our results suggest that a susceptibility gene for GD (GD-1) is localized near D14S81. The close proximity to MNG-1 may suggest that this gene region may influence the genetic susceptibility to a variety of thyroid disorders.

Pregnancy Suppresses the Development of Mouse Thyroiditis by Enhancing Th2 Responses. L. Ahmad[1], M. Kita[1], P. Unger[2], and T.F. Davies[1]. [1]Division of Endocrinology and Metabolism, Department of Medicine and [2]Department of Pathology, Mount Sinai School of Medicine, New York, NY.

Many human autoimmune diseases, including autoimmune thyroid disease, are affected by pregnancy. These immunological changes include a reduction in cell-mediated immunity (Th1) and enhancement of humoral immunity (Th2) T cells. To investigate the influence of pregnancy on the development of thyroglobulin (Tg)-induced experimental autoimmune thyroiditis (EAT), we examined the intrathyroidal histological changes during pregnancy and the postpartum period. Twenty female CBA/J mice were immunized with Tg (50 ug) IV. Three hours later, they were injected with lipopolysaccharide (LPS) (20 ug) IV. Twenty female control mice were injected with LPS only. Ten Tg-immunized mice and 10 control mice were mated one week after the second immunization and sacrificed three weeks later. Serum was collected for Tg antibody levels. Thyroid histology by H&E staining was graded as follows—0.5: small focal areas of inflammatory cells; 1.0: focal collections of mononuclear cells with some follicular destruction; 2.0: diffuse infiltration of thyroid follicle involving approximately 40% or less of thyroid tissue examined; 3.0: destruction of 40%–80% of thyroid tissue; and 4.0: destruction of more than 80% of thyroid tissue. A thyroiditis severity index (TI) was calculated as the mean group grade x number of mice affected. In the pregnant Tg-immunized mice, 2/7 (28.6%) developed thyroiditis (TI = 1.5) whereas 5/10 (50%) of the non-pregnant Tg-immunized mice developed thyroiditis (TI = 5.4). All mice immunized with Tg showed high titers of anti-Tg in their serum, with no significant differences between groups. In a separate experiment, EAT was induced in 20 pregnant and 20 non-pregnant mice. At 2 weeks postpartum (7 weeks after immunization), 2/10 (20%) of the pregnant EAT mice had thyroiditis compared to 6/10 (60%) in the non-pregnant EAT mice (also 7 weeks after immunization) (TI = 2.5 and 5.0, respectively). Tg-stimulated splenocyte release of interferon g (IFN-g) was similar in pregnant and non-pregnant EAT mice. In contrast, Tg-stimulated splenocyte release of interleukin-4 (IL-4) was 182% of baseline in pregnant EAT mice compared to 12% in non-pregnant EAT mice. We conclude that the severity of EAT was markedly reduced by pregnancy and that pregnancy suppressed the induction of EAT. This suppression was associated with enhancement of a Th2 phenotype as shown by the increase of IL-4 production.

TSH Receptor Multimeric Complexes. P.N. Graves, A. Pritsker, and T.F. Davies. Division of Endocrinology and Metabolism, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Maturation of the thyroidal thyroid-stimulating hormone receptor (TSHR) is thought to involve posttranslational cleavage(s) of the holoreceptor into two similar length fragments, designated a and b subunits. These remain associated via disulfide bonds or may dissociate into shed a (ectodomain) and retained b (transmembrane) fragments. Evidence supporting these assumptions comes mainly from observations on TSHR-transfected cells, rat thyrocyte lines, and primary thyrocyte cultures, and is substantiated in thyroid tissue immunoblots by detection of the predicted fragments using antibodies specific for either subunit. However, the tissue immunoblots revealed additional and unexpected complexity. These included the presence of uncleaved holoreceptors and of both subunits not linked to each other by disulfide bonds. Both the holoreceptors and TSHR-b subunits were present as monomers and as apparent disulfide-linked homodimers. Additional studies revealed two populations of TSHR-b monomers of apparent molecular masses 52 kd and 47 kd. These were consistent with two holoreceptor cleavage sites in the regions 300–320 (site 1) and 360–380 (site 2), respectively. These proposed sites flank 50 residues (317–366) unique to the TSHR, i.e., they are absent from other glycoprotein hormone receptors and provide a mechanism for its excision. However, the consistent presence of TSHR-b52 and absence of TSHR-b47 from some preparations indicated preferential cleavage at site 1. A consequence was retention of the 50 residue "insert" in all or some TSHR-b subunits in all preparations analyzed. In summary, TSH receptors on thyroid plasma membranes comprise discrete populations of processing variants whose role(s) in normal thyroid physiology and thyroid autoimmunity await further clarification.

CK-MB Release in Diabetic Patients Following Coronary Intervention. J.P. Crandall, R.R. Vidhun, S. Chockalingham, K.L. Leibowitz, G. Dangas, and J.A. Ambrose. Department of Medicine, Division of Endocrinology, Mount Sinai School of Medicine, New York, NY.

Patients with diabetes undergoing multivessel angioplasty have a higher mortality on follow-up in comparison to coronary bypass surgery, in addition to a higher rate of restenosis. Sulfonylurea therapy may also be associated with increased cardiovascular mortality. The acute outcome of coronary intervention in diabetic subjects as well as the relationship to metabolic control is unknown.

Methods: Ninety-seven patients with diabetes undergoing intervention had glycosylated hemoglobulin (HbA1C) levels and fasting glucose drawn prior to intervention. Creatine kinase MB bond (CK-MB) levels were measured routinely post-procedure at 8 and 16 hrs, and compared to 579 non-diabetic controls undergoing intervention during the same time period. Demographic, clinical and procedural characteristics including the use of ReoPro (abciximab) and interventional modality, were similar between groups. Any CK-MB elevation was 17.9% vs 20.4% in diabetics vs non-diabetics respectively (p = NS). CK-MB elevation > 3x normal was 3.2% vs 4.7% respectively, (p = NS).

Ambient blood glucose and HbA1C levels in diabetics did not correlate with CK-MB elevation post-procedure. Sulfonylurea use (67% of diabetics) was not associated with higher incidence of CK-MB release.

Results: Thus, patients with diabetes do not appear to have a higher incidence of CK-MB release following coronary intervention.

Furthermore, metabolic control and therapy with sulfonylureas do not appear to correlate with CK-MB elevation. Any relationship between these metabolic variables and long-term outcome (mortality or restenosis) remain to be explored.

A Confocal Microscopic Study of Synaptophysin Immunoreactive Contacts onto GnRH Neurons in Mice. G. Rajendren, and M.J. Gibson. Division of Endocrinology, Mount Sinai School of Medicine, New York, NY.

Experiments were carried out to investigate synaptophysin (a specific marker for presynaptic terminals) immunoreactive (IR) contacts onto gonadotropin-releasing hormone (GnRH) neuronal cell bodies in female mouse brain. Brain sections were immunofluorescently labeled for synaptophysin and GnRH. From each brain two coronal sections, one passing through anterior septum (anterior section) and the other passing through organum vasculosum of lamina terminalis (OVLT) (posterior section), were selected and were analyzed under confocal laser scanning microscope. Images were collected at an interval of 1 mm from each GnRH cell, and the stack of images obtained from each cell was analyzed for synaptophysin IR contacts. GnRH cells located at the anterior part of the brain received only half as many synaptophysin IR contacts as compared with those located at the level of OVLT. Thus, the results suggest that the density of synaptic input to the GnRH cells may depend on the location of the cell in the brain.

Androgens Increase the Production and Secretion of Vascular Endothelial Cell Growth Factor by Human Prostate Fetal Fibroblasts. A. Kirschenbaum[1], X.-H. Liu[1], P.D. Greenberg[2], S.A. Aaronson[3], J.F. Holland[3], and A.C. Levine[2]. [1]Department of Urology and [2]Division of Endocrinology and Metabolism, Department of Medicine, [3]Derald H. Ruttenberg Cancer Center, Mount Sinai School of Medicine, New York, NY.

Introduction and Objectives: Human fetal prostate development is known to be dependent upon androgens and stromal-epithelial interactions. Vascular endothelial cell growth factor (VEGF) is an endothelial cell-specific mitogen which is critical to normal vasculogenesis. We determined the cell-specific expression of VEGF in the human fetal prostate and studied its androgenic regulation in prostate fetal fibroblasts.

Methods: Fetal prostates were derived from 17 22 week gestation fetuses. Immunohistochemical staining for VEGF expression was carried out on formalin-fixed tissues. Human prostate fetal fibroblasts were grown in culture ± the addition of dihydrotestosterone (DHT 10-10-10-6M) and VEGF mRNA and protein levels determined by Northern blot and Western blot, respectively. VEGF mRNA transcription rates in the fibroblasts ± DHT were determined by Nuclear Run-On Assay.

Results: Immunohistochemical studies localized VEGF protein expression to the stromal cells of the developing prostate. DHT upregulated VEGF mRNA and both the cell-associated and secreted isoforms of VEGF within 12–24 hours. Maximal upregulation (> 2-fold) of VEGF expression was demonstrated with DHT 10-8 M. Nuclear run-on assay demonstrated that the increase in VEGF expression was at least partially due to increased VEGF mRNA transcription which was maximal 2 hrs after DHT addition.

Conclusions: VEGF is expressed by the stromal cells of the human fetal prostate. VEGF expression by human prostate fetal fibroblasts is under androgenic regulation. Androgens influence prostate development via effects on vasculogenesis.

Contrasting Genetic and Environmental Influences on the Development of GD and GO. A.M. Inzerillo[1], G. Barbesino[1], Y. Tomer[1], M. Meltzer[2], E. Concepcion[1], D.A. Greenberg[3], and T.F. Davies[1]. Departments of [1]Medicine, [2]Ophthalmology, and [3]Psychiatry, Mount Sinai School of Medicine, New York, NY.

Graves' Disease (GD) is an autoimmune thyroid disease (AITD) characterized by hyperthyroidism and by the occurrence of a distinctive ophthalmopathy, Graves' ophthalmopathy (GO), which presents with markedly varying degrees of severity. GD clusters in families but the importance of inheritance in the pathogenesis of the associated GO is unclear. We have studied family history of AITD in 54 consecutive patients with severe GO, as defined by scoring at least class IIIa in Werner's classification. Patients were selected by unambiguous single ascertainment. The mean age at onset of GO was 43 years (range 20–78) and 74% were women. Thirty-eight patients were Caucasians (70%), 12 (22%) African-Americans, 3 (6%) Hispanic and 1 (2%) Asian. Only 3 of the patients were initially diagnosed with Hashimoto Thyroiditis (HT). No patients had the diagnosis of euthyroid Graves' disease. The diagnosis of GO was made in 51 patients concurrently with the diagnosis of AITD. Eleven patients (20%) were treated with antithyroid medications alone, 39 (72%) radioactive iodine and 3 (6%) surgery. Forty (74%) of the patients were on T4 replacement. Fifty-nine percent of patients were smokers at diagnosis of GO. Twenty-two (41%) had a family history of AITD, defined as a first degree (in 18 cases) and/or a second degree (9 cases) relative affected with either GD or HT. The segregation ratio for AITD in our ascertained GO families was 0.100 overall and 0.143 in females, in keeping with a higher penetrance of AITD in women. In 9 families, HT was observed, in 4 families both HT and GD, and in 9 families only GD. Importantly, only 2 of the 54 patients had a family history of severe GO (requiring active treatment). Hence, the high prevalence of AITD among relatives of GO patients agreed with the known presence of a genetic predisposition to AITD and this predisposition was stronger in women than in men. However, these data did not support a major role for familial factors in the development of severe GO. In an ethnically homogeneous subgroup of the GO patients, 38 Caucasian individuals, we performed an association study. We looked for an association at the three candidate loci (CTLA-4, thyroid-stimulating hormone [TSH-R], and tumor necrosis factor [TNF b]). Results were compared by c2 analysis with 61 ethnically-matched controls. No association was found with any of the selected candidate genes and GO. We conclude that environmental factors, rather than major genetic influences, are more likely to predispose certain individuals with AITD to the severe form of GO.

Human Thyroid Organoid Formation in Simulated Microgravity: The Essential Role of KGF. A. Martin[1], A. Zhou[1], R. Gordon[2], A.E. Schwartz[3], E.W. Friedman[3], and T.F. Davies[1], Departments of [1]Medicine, [2]Pathology and [3]Surgery, Mount Sinai School of Medicine, New York, NY.

We have used simulated microgravity (MG), provided by a NASA-developed bioreactor, to generate artificial human thyroid tissues containing multiple thyroid neofollicles in serum-free medium. To enhance the low-shear environment even further, we increased the medium viscosity with a diluted (3% v/v) suspension of extracellular matrix basement membrane extract (BME). We observed that under these conditions, recombinant human keratinocyte growth factor (KGF) 7 n/mL supported the survival and differentiation of the human thyrocytes. Morphologically, there were fully-differentiated thyroid neofollicles with correctly oriented mictrovilli and intercellular desmosomal junctions which were surrounded by a basement membrane after a 2-week culture period (follicle # 20.8, range 18–42, per available tissue). The addition of KGF caused multiple aggregation of thyrocytes within 6–18 hours to form an artificial "organoid." Thyroid follicles were located in close proximity to each other and had a polarized appearance. Immunogold labeling using a primary antibody to human thyroglobulin showed staining of the follicular lumina and secretory vesicles, and increasing levels of human thyroglobulin were detected in the culture media. In contrast, control gravity cultures of thyroid cells developed as monolayers. Culture under simulated MG thus allowed direct visualization of thyrocyte/extracellular matrix interaction. Measuring cell proliferation (total DNA) in simulated MG showed a marked increase (170%) in KGF, MG-cultured cells. Such MG-generated, KGF-maintained, artificial human thyroid organoids closely resembled natural thyroid tissue and will enhance the study of human thyroid disease.

Insulin Use, the Performance of Processes of Care, and Risk of Hospital Admission for DM Patients on Dialysis. C. Levy. Division of Endocrinology, Mount Sinai School of Medicine, New York, NY.

Missed Opportunities to Improve Diabetes Self Care Skills When Patients with Diabetes Are Hospitalized for Other Reasons. S.H. Roman[1], S. Haddow, M.R. Chassin. [1]Department of Medicine, Division of Endocrinology, Survey Center, and Department of Health Policy, Mount Sinai School of Medicine, New York, NY.

Why Do Patients Having Finger-Stick Glucoses While Hospitalized Deny Diabetes? E.M. Brett, S.H. Roman. Department of Medicine, Division of Endocrinology, Mount Sinai School of Medicine, New York, NY.

Increased Blood Thrombogenicity in Diabetes Mellitus. J.P. Crandall, U. Rauch, S.H. Roman, J.T. Fallon, S. Jayaramon, and J.J. Badimon. Department of Medicine, Divisions of Endocrinology and Cardiology, Mount Sinai School of Medicine, New York, NY.

***In Vitro* Evidence That a Medialbasal Hypothalamus (MBH)-Derived Soluble Factor Directs GnRH Axonal Outgrowth.** M.J. Gibson, and L. Ingraham. Department of Medicine, Division Endocrinology and Metabolism, Mount Sinai School of Medicine, New York, NY.

Gastroenterology

* **High Prevalence of Gastrointestinal Symptoms in Fabry's Disease.** L. Fiedler, P. Ashton-Prolla, C. Eng, and M.W. Babyatsky. Departments of Medicine and Human Genetics, Mount Sinai School of Medicine, New York, NY.

Adenocarcinoma of Small Intestine in AIDS Patients. K.V. Ramasamy, R. Singh, J. Baum, and V. Gumaste. Department of Gastroenterology, Elmhurst Hospital Center, Elmhurst, NY and Department of Gastroenterology, Mount Sinai School of Medicine, New York, NY.

Background: Adenocarcinoma is the most common small bowel malignancy. It has an incidence of 3.9 cases per million persons per year. Most patients are in their 50s or 60s. In AIDS patients, there is increased incidence of small bowel lymphoma. We describe an usual presentation of small intestinal adenocarcinoma in a patient with AIDS.

Case: A 42-year-old patient with AIDS (CD4 count 38) was admitted with acute onset of passing large amount of bright red blood per rectum. He denied vomiting. He was hypotensive (systolic BP 80) and tachycardiac (heart rate 130) in ER. Abdomen was soft and no masses were palpable. Rectal examination revealed bright red blood. Nasogastric aspirate drained bilious fluid. His initial Hb was 8.1 gm%. He was resuscitated and the flexible sigmoidoscopy revealed pale mucous and could not proceed beyond rectosigmoid. The superior mesenteric and inferior mesenteric angiogram did not reveal any gross vascular abnormality or active bleeding. Upper GI endoscopy revealed only mild antral gastritis. The CT scan of the abdomen and pelvis did not reveal any abdominal or pelvic mass. Small bowel series revealed partial jejunal obstruction. Push enteroscopy revealed at 80 cm in the small intestine a friable large irregular mass almost obstructing the lumen. The histopathology of the biopsy specimen was reported as intraepithelial adenocarcinoma. No invasion was demonstrated in the specimen. Numerous cytomegalovirus (CMV) inclusions were seen in stroma. Patient developed vomiting and abdominal pain, and was scheduled to go for laparotomy but he deteriorated and died.

Discussion: There is an increased incidence of malignant neoplasams in HIV-infected patients. Some malignant tumors have undoubted relationship with HIV infection. Non-Hodgkin's lymphoma (NHL) is the most common malignant small bowel neoplasm in patients with AIDS. Adenocarcinoma is the most common malignant small bowel neoplasm in non-AIDS patients. Adenocarcinoma of lung in HIV-infected patients was reported to follow a more aggressive course. Studies on adenocarcinoma of small bowel in AIDS patients is lacking in the literature. This case illustrates aggressive nature of this tumor in AIDS patients and unusual presentation of massive lower GI bleeding. The association of CMV infection in this tumor is not clear. In AIDS patients, even though NHL is the most common small bowel malignant tumor, adenocarcinoma should also considered in the differential diagnosis which can follow aggressive course.

Environmental Noise Alters Gastric Electrical Activity: Effect of Age. J.S. Castle[1], M.R. Warner[1], and M.A. Korsten[1,2]. [1]Medical Program and Audiology Service, Bronx VA Medical Center, Bronx, NY; and [2]Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Purpose: Previous work has indicated that loud environmental noise, especially on our streets, in hospitals, and in other public places may contribute to a wide range of health problems. Specifically, studies have shown a deleterious effect of auditory stimuli on gastrointestinal function. We therefore undertook a study that assessed the effect of noise on gastric electrical activity, a relationship which has not heretofore been delineated. In addition, we studied the effect of noise on blood pressure, since we suspected that these two parameters might be interrelated.

Methods: A total of 21 male subjects (range 22–71 yrs, mean 44 yrs) were recruited. Participants were studied in an enclosed sound room and exposed, in a random order, to 4 conditions (3 auditory stimuli and a period of silence). All periods lasted 10 minutes and were interspersed with 10 minutes of silence. The three auditory stimuli were as follows: (1) hospital noise (ambient noise in an SICU) played at a volume of 87.4 dBA (time weighted average of volume); (2) conversation babble (Auditec of St. Louis, MO) played at 91.3 dBA; and (3) traffic noise (Columbus Circle, New York, NY) played at 85.6 dBA. Blood pressure was monitored every 5 minutes using an automatic blood pressure recording device. The electrogastrogram (EGG) was obtained using a Synectics Microdigitrapper connected to three electrodes placed percutaneously on the anterior wall of the abdomen.

Results: The average percentage of 3 cycle per minute (CPM) activity decreased during exposure to hospital noise (12.0%, $p < 0.05$), traffic noise (13.9%, $p < 0.02$), and conversation babble (7.1%, p = NS). Since gastric electrical activity changes with age, we further analyzed the effect of age on this phenomenon. To this end, subjects were divided into two groups, those less than 50 years of age ($n = 12$), and those more than 50 years of age ($n = 9$). Subjects in the younger group showed a consistent reduction in 3 CPM electrical activity during hospital noise (22.9%, $p < 0.02$), traffic noise (19.0%, $p < 0.02$), and conversation babble (15.5%, p = NS). These observations were accompanied by a significant increase in bradygastria activity (slower than 3 CPM): hospital noise, ($p < 0.02$) and traffic noise ($p < 0.05$). In contrast, subjects more than 50 years of age did not exhibit a significant decrease in 3 CPM electrical activity. Regardless of age, noise did not alter blood pressure or heart rate.

Summary and Conclusion: Under the present conditions, loud noise altered the EGG in younger individuals but had no effect on blood pressure. To the extent that these changes in the EGG lead to alterations in gastric function, our data indicate that environmental factors, specifically noise, may have adverse physiological sequelae.

Endoscopic Band Ligation as an Effective Modality for Hemostasis in Dieulafoy's Lesion. A.M. Jiminez, J.A. Galan, M.J. Martino, and W.J. Baddoura, Department of Gastroenterology, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Introduction: Dieulafoy's lesion is a caliber-persistent artery which is just deep to the muscularis mucosae in the gastrointestinal tract. It is recognized as a potential, albeit rare, cause of hemodynamically significant upper gastrointestinal hemorrhage. Several endoscopic modalities have been described in the literature for achieving hemostasis.

Case Report: We present a 56-year-old male admitted for gross hematemesis. He had a history of hypertension. There was no complaint of abdominal pain or melena. The first episode was coffee ground material followed by fresh blood. Social history was remarkable for daily alcohol consumption and tobacco smoking for 40 years. There was no significant history of NSAID or aspirin intake. Blood pressure was 150/102 mm Hg and heart rate 104/min. Physical exam was remarkable for black stool. The abdominal exam was benign. Hemoglobin and hematocrit were 9.0 g/dL and 27.8%, respectively. Prothrombin and partial thromboplastin times were normal. Endoscopy was performed 12 hours after presentation and revealed an actively bleeding vessel in the proximal body with no surrounding mucosal ulceration. This was consistent with Dieulafoy's lesion. Attempts to control the bleeding with epinephrine injection and electrocoagulation were unsuccessful. Hemostasis was finally achieved by using endoscopic band ligation (EBL). Endoscopy was performed 3 days later and revealed that the band was still in place with no active bleeding. The patient did well and was discharged with no further bleeding.

Conclusion: EBL is an effective and safe modality for the control of variceal bleeding. It can also be used successfully for Dieulafoy's lesion after standard therapeutic measures have failed.

Chronic use of aspirin or warfarin does not increase the rate of positive fecal occult blood test (FOBT). Comparison of three methods of FOBT. A. Weiss, E. Feit, J. Castle, S. Itzkowitz. Division of Gastroenterology, Mount Sinai School of Medicine, New York, NY.

Health Related Quality of Life (HRQOL) in Patients after the Ileoanal Pull-through Procedure (IAPT). M. Blam, M. Bari, C. Brauer, T. Heimann, S. Gorfine, and A. Weiss. Department of Medicine, Division of Gastroenterology, and Department of Surgery, Mount Sinai School of Medicine, New York, NY.

Immunoreactive Cyclooxygenase-2 Expression in Ulcerative Colitis-Associated Neoplasms (UCANs). A. Weiss, N. Harpaz, A. Chen, A. Vergara, N. Medalie, and S. Itzkowitz. Department of Medicine, Division of Gastroenterology, and Department of Pathology, Mount Sinai School of Medicine, New York, NY.

Interleukin-10 Stimulates Somatostatin Gene Expression *in Vitro* and *in Vivo*. J. Morton, P. Jiang, H. Wasserstrom, S. Mehta, J. Lawler, A. Francella, and M.W. Babyatsky. Department of Medicine, Division of Gastroenterology, Mount Sinai School of Medicine, New York, NY.

Expression of Sucrase-Isomaltase and Intestinal Trefoil Factor in Metastatic Colon Carcinoma. M. Babyatsky, A. Chen, P. Jiang, J. Lin, M. Schwartz, and S. Itzkowitz. Department of Medicine, Division of Gastroenterology, and Department of Surgery, Mount Sinai School of Medicine, New York, NY.

General Medicine

Physicians' Attitudes and Knowledge Toward Pharmaceutical Costs. S. Reichert[1], T. Simon[1], and E. Halm[1,2]. [1]Division of General Medicine, and [2]Department of Health Policy, Mount Sinai School of Medicine, New York, NY.

Objective: To determine resident and attending physicians' knowledge of, familiarity with and attitudes toward the cost of commonly prescribed medications.

Methods: Survey of 144 internal medicine housestaff and 44 general medicine attending physicians at a tertiary care academic medical center.

Results: One hundred and thirty-four of 189 physicians responded (71% response rate). Levels of experience: 22% PG-1, 21% PG-2, 27% PG-3, and 30% attending physician. Fifty-five percent of respondents were male.

Eighty-eight percent of respondents felt cost was an important consideration when making medication choices, yet 80% felt often unaware of the actual costs. Only 13% of respondents stated they had formal education relating to the cost of medications. Thirty-three percent had easy access to sources that provide the cost of medications. Sources identified as most often used were: The Medical Letter (65%), other physicians (52%), patients (45%), pharmacists (41%), pharmaceutical representatives (25%), and advertisements (17%). Seventy-one percent surveyed were willing to sacrifice some degree of efficacy in order to make drugs more affordable for their patients and only 8% preferred brand name medications. Only 16% always or often ask their patients about the cost of medications.

Considering a patient's insurance: 94% gave strong consideration to the cost of medications when patients were self-pay, 68% when patients had Medicare, and 30% when patients had Medicaid or were participants in an HMO with a prescription plan.

In comparative analysis: residents were 3.4 times more likely than attendings to report being unaware of actual costs of medications (Odds Ratio [OR] 3.42, 95% confidence interval [CI] 1.49 – 7.87). Attending physicians were more likely to access the Medical Letter (OR 2.3, CI 1.01 – 5.4), pharmacists (OR 3.5, CI 1.7 – 7.5) or pharmaceutical sales representatives (OR 2.13, CI 0.9 – 4.8) than residents. Residents were more likely to use other physicians as sources (OR 3.8, CI 1.73 – 8.13). Finally, attending physicians were 3 times more likely to consider cost for Medicare patients than residents (OR 3.06, CI 1.257.47).

Discussion: While most physicians feel strongly that cost is an important factor when choosing medication; most are often unaware of the actual costs. Few physicians apparently have ready access to drug costs. Attending physicians were more likely to use the medical letter, a pharmacist or drug representatives. Dependence on salesmen for drug information, while infrequent, is worrisome. Residents, not surprisingly, relied more often on other physicians (presumably attendings).

Since most physicians are willing to sacrifice efficacy and few prefer brand name medications, one might hypothesize that if educated, physicians would choose less expensive, generic drugs. Among resident physicians, there appears to be lesser concern about costs to those patients covered by Medicare in which the medications are paid for directly by the patient..

Quality Improvement in Prescription Renewal Service in an Underserved Urban Primary Care Practice; 1998. S. Jimenez, and R.A. David. Ambulatory Care Department, Elmhurst Hospital Center, Elmhurst, NY.

Objective: Varied practice patterns are notable regarding renewing of prescriptions in clinic settings. Our primary care practice is located in a medically-underserved urban setting and is multi-cultural. We were interested in evaluating whether our current practice of renewing prescriptions for "walk-in" patients was consistent with high quality of care. The benchmark of quality care was that patients would only receive medication that was intended by the primary ordering physician to last until the next suggested evaluation by that physician.

Methods: A patient survey was created, pilot tested, and then utilized with patients presenting solely for medication renewal. It was administered verbally in Spanish and English by a medical provider prior to offering the prescription renewals to "walk-in" patients who belonged to the practice. Patients were asked why they were presenting for a prescription renewal in a "walk-in" service.

Results: Over a 7-week study period, 210 of 678 patients presenting for medication refills were sampled. Data was collected from all 210. Of these patients, 34% + 6% ($p < 0.05$) indicated that they needed a prescription because they missed their appointment with their physician; 61% + 6% ($p < 0.05$) patients had not seen their physician for more than 6 months and 84% + 5% ($p < 0.05$) had not seen their physician in more than 3 months. Of these patients, 11% + 5% ($p < 0.01$) cited issues including that they had received the medicine in another country; that they had taken the wrong dose of medicine so they ran our early; and that their generic medicine didn't seem to be working. While 43% + 7% ($p < 0.05$) of patients indicated that their physicians had not given them enough medication to last until their next appointment, they in fact were found to have valid prescriptions on file with the pharmacy.

Conclusions: A large proportion of patients presenting for renewal of medication either: (1) really needed a medical evaluation, or (2) needed only to be directed to the pharmacy for a medication refill. Subsequent to analysis of our results, we instituted significant changes in our medication renewal policy. Patients are initially identified as to whether they have valid prescriptions in the pharmacy. All other patients are now formally evaluated by a medical provider before they are given a prescription renewal. These focused evaluations are targeted to the particular organ system being treated by the ordered medication. Patients are then given a choice of follow-up with the provider giving them their prescription renewal or with their former primary provider.

Subclavian Steal and Antiphospholipid Syndrome: A Rare Combination. K. Chennapragada, V.M.K. Bhaskarabhatla, M. Knee, and N. Elrabie. Department of Internal Medicine, St. Joseph's Hospital and Medical Center, Paterson, NJ.

The antiphospholipid syndrome (APS) is an immunological disorder in which arterial or venous thrombosis or both may occur in patients with antiphospholipid antibodies. Other clinical features of APS include livedo reticularis, skin ulcers, and miscarriages. There are reports describing thrombosis of the coronary, cerebral and pulmonary arteries in patients with APS. Nevertheless, subclavian steal syndrome (SSS) resulting from subclavian artery thrombosis was not reported previously in patients with APS. We report a case of a 42-year-old woman of with long-standing systemic lupus erythematosus (SLE), antiphospholipid antibodies, livedo reticularis, multiple miscarriages, and hypertension. She presented with several months' history of progressively worsening symptoms of episodic dizziness and pain in left arm associated with weakness whenever she used her left hand. Her primary care physician noticed a thrill in her neck and referred her to this tertiary hospital for further assessment. On examination, she had asymmetric arterial pulses and pressures in the upper extremities, a palpable thrill and an audible bruit over the left subclavian artery. Angiography confirmed total occlusion of the left subclavian artery, reversal of the blood flow to the vertebral artery and ischemia of the left arm combined with dizziness upon exercise, supporting a diagnosis of SSS. An urgently performed carotid-subclavian artery bypass reestablished the distal radial pulses and resulted in good functional outcome. Here, we have a young woman with the complicated APS who wants to have more children. Over the past 8 months following the arterial bypass surgery, she had been free of thrombotic events while on low-dose aspirin, prednisolone, nebumetone, and diltiazem.

Application of a Weight-Based Heparin Dosing Nomogram for Patients with Unstable Angina Pectoris: Preliminary Data from an Urban Medical Center. J.C. Gil-Olaya, M. Santos, and R. Solis. Department of Medicine, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Objective: To study the effect of heparin dosing (Hd) by the use of a weight-based nomogram, and to compare the anticoagulation achieved using that regimen with that obtained using an older therapeutic protocol.

Setting: An 800-bed, tertiary-care, urban teaching hospital.

Design: Prospective application of the Hd protocol under study to a group of 15 patients with unstable angina pectoris (UAP) enrolled over a 3-month period. Extent of anticoagulation was determined by partial thromboplastin time (PTT). These data were compared with those from an historical group of 71 UAP patients from the same institution who received Hd based on an older protocol.

Results: Of the 11 patients who completed the study, 7 (64%) achieved the therapeutic threshold (based on consensus values for PTT) compared with 22.5% (16/71) who were determined to be adequately anticoagulated via the older protocol ($p = 0.009$, Fisher's exact test).

Conclusions: These data suggest that the application of a weight-based protocol for Hd may facilitate the achievement of proper anticoagulation in patients with UAP.

Is Flexible Sigmoidoscopy Adequate Colorectal Cancer Screening for African-Americans? G. Emili, and S.J. Daniel. Department of Medicine, North General Hospital, Mount Sinai School of Medicine, New York, NY.

Colorectal cancer is the most preventable GI cancer, if adequate screening is done. Flexible Sigmoidoscopy (Flexsig) is unlikely to be adequate screening in African-Americans who appear to have high incidence of right-sided lethal cancers.

Purpose: To evaluate the effectiveness of screening flexsig in our hospital populations which is largely African-American and Latino.

Methods: Data was collected by reviewing cancer records at our hospital from January 1990–December 1996, noting all colorectal cancers diagnosed, anatomical sites, race, age of patients and stages of disease. Records of all flexsigs done from 1992–1996 were also reviewed. Number of patients visiting North General Hospital Clinics, 50 years and older, between 1993 and 1996 were also obtained.

Results: There were 8,642 patients seen between 1993 and 1996 for 103,977 clinic visits, and 326 underwent flexsig. Of the flexsig, 264 were normal, 39 incomplete due to poor prep, 23 abnormal, 8 adenomatous polyps, and 14 hyperplastic polyss polyp with 1 adenocarcinoma *in situ*. The cancer register revealed 99 cases from January 1990–December 1996: 42 occurred in right colon and 57 were in the left colon. Of the cancers, 51 were Late Stage, of which 28 occurred in the right colon and 23 in the left colon. Of all right-side cancers, 38 occurred in African-Americans and 4 in the Latino population. Of the advanced cancers on the right, 27 occurred in African-Americans and 1 in the Latino population.

Conclusion: Flexsig is capable of missing 42% of all colorectal cancers, the majority of which are of the advanced stage. Flexsig appear ineffective in African-American population.

Geriatric AIDS Population Study (GAPS) of an Inner City Population in the United States. C. Smith[1], S.S. Shah[2], J.P. McGowan[3], S. Blum[3], E.E. Telzak[3], A. Malik[3], and R.S. Klein[2]. [1]Department of Medicine and the AIDS Center, Mount Sinai School of Medicine, New York, NY; [2]Montefiore Medical Center, Bronx, NY; and [3]Division of Infectious Disease, The Bronx Lebanon Hospital Center, Bronx, NY.

Objectives: To describe the demographics, clinical status and primary care of an older HIV/AIDS population at three New York City HIV clinics.

Design: Retrospective chart review.

Methods: The medical records of 126 patients older than 55 years of age were reviewed. Gender, ethnicity, HIV risk factors, AIDS defining conditions, comorbid conditions and documentation of preventive care were abstracted.

Results: The gender and ethnicity were: 69% male; 53% African-American (non-Hispanic), 45% Hispanic, 2% Caucasian. Median age was 58 (55–80) years. Forty-eight percent of individuals irrespective of gender, and 44% of males, reported heterosexual contact (HSC) as their risk factor. Other risk factors included: injecting drug use (30%), men having sex with men (7%), and blood transfusion (3%). Sixty-four percent had AIDS defining conditions (44% were solely by CD4 count $< 200/\text{mm}^3$). Other AIDS defining conditions by frequency were: PCP (29%), wasting (20%), *Candida esophagitis* (20%), CMV (11%), HIV encephalopathy (9%), and others (11%). Median duration of follow-up was 26.5 (0–113) months. The patients had a mean of 2.1 comorbid conditions which included hypertension (37%), chronic obstructive pulmonary disease/asthma (32%), diabetes mellitus (18%), and coronary artery disease (10%). The proportion of individuals with documented annual preventive care was: mammogram (54% of females), Papanicolaou's smear (72% of females), digital rectal examination (35%), serum cholesterol (86%), tuberculin skin testing (80%), and influenza vaccination (89%). Documentation for pneumococcal vaccination and minimental status examination were 88% and 4%, respectively.

Conclusions: Our findings of heterosexual contact as the major risk factor demonstrate a greater need for education of inner city geriatric populations and health care providers with regard to high risk sexual behavior and HIV screening. As the number of older individuals with HIV increases, health care providers must emphasize general medical preventive strategies and neuro-psychiatric evaluation.

Diagnosis of Diabetic Nephropathy in the General Medical Clinic of Mount Sinai Hospital and Medical Center. C.B. Miller. Internal Medicine Associates, Mount Sinai School of Medicine, New York, NY.

Diabetic nephropathy due to Type 2 Diabetes is now the main cause of end-stage renal disease in the United States. Early detection and treatment may ameliorate the course of this disease. The recommendations of the National Diabetes (ADA) and nephrology societies call for a minimum of one yearly measurement of both serum Creatinine (SCr), and urine albumin or microalbumin excretion by precise quantitative methods (PQT). We studied compliance by the physicians of the General Medical Clinic (GMC) comprising 120 medical residents and 22 general medicine attendings. The majority of patients are Latino or African-American, urban and poor.

We analyzed the computerized laboratory records of patients seen in the GMC over a one-year period (1997). Patients with a glycosylated hemoglobin (HBA1c) ≥ 6% (Diabetic range) or 2 random glucose of more than 200 mg/dL were identified as Diabetic (1734 pts).

The frequency of testing for urine protein performed either by semi-quantitative method, urine dipstick (UDip), or by precise quantitative tests (PQT), was measured and compared in 2 groups of patients separated according to their level of serum creatinine (SCr) into "normal" group: SCr <1.4 mg/dL and "high" group: SCr ≥ 1.4 mg/dL.

Results:

TABLE 1

All GMC diabetic patients (1734 Pts).

Urine tests	Any Urine Protein Test Performed	Routine Urine Protein Dipstick Only (Udip)	Precise Urine Quantitative Protein Tests (PQT)	Both Urine Dip and PQT Performed	No Urine Tests Performed
Normal SCr < 1.4 mg/dL 1447 patients = 83%	70%	46%	12%	58%	30%
High SCr ≥ 1.4 mg/dL 287 patients = 17%	79%	64%	10%	71%	21%

TABLE 2
Renal data in 626 GMC diabetic patients (36% of all pts) who had a PQT performed:

Urine Albumin Excretion	Normal Micro Albumin (< 30 mcg/24 hr)	Clinical Range Albuminuria (> 300 mg/24 hr)	Nephrotic Range (>3 g/24 hr)
Normal SCr < 1.4 mg/dL	81%	19%	13%
High SCr ≥ 1.4 mg/dL	34%	76%	65%

In conclusion, this study shows:

There was a very high prevalence of renal function abnormalities in this population. Renal insufficiency (SCr ≥ 1.4 mg/dL) was present in 17% (287) of all GMC diabetics. In the "normal" SCr group (< 1.4 mg/dL), if one were to extrapolate the results from Table 2, it is estimated that an additional 19% (300 pts) would have proteinuria in the clinical range (> 300 mg/24 hr). Thus 587 or 31% of all GMC diabetics have potentially significant renal damage.

The GMC physicians did not adhere to ADA guidelines for ordering urine protein tests, especially for ordering MicroAlbumin (10–12% of pts). Unexpectedly, adherence was no higher in the group of patients with "high" serum creatinine.

An educational intervention for improved detection and treatment of diabetic nephropathy has been instituted in the GMC.

Hematology

*** Synergy Between Anti-Sense RNA Inhibition of Stathmin Expression and Taxol in the Gene Therapy of Cancer.** C. Iancu, S. Mistry, and G.F. Atweh. Department of Medicine, Division of Hematology, Mount Sinai School of Medicine, New York, NY.

Stathmin is a cytosolic phosphoprotein that is expressed at very high levels in different types of transformed cells. Studies of this protein in several laboratories including our own showed that stathmin is a target for cdc2 kinase and demonstrated a role for its expression and phosphorylation in the regulation of mitosis in eukaryotic cells. The major mitotic function of stathmin in eukaryotic cells is to regulate the dynamics of the mitotic spindle by enhancing microtubule depolymerization. We had previously shown that inhibition of stathmin expression in K562 leukemic cells by anti-sense RNA results in a marked abrogation of the malignant phenotype as determined by *in vitro* and *in vivo* assays in SCID mice. Taxol is a new chemotherapeutic agent that is highly effective in the treatment of several neoplastic disorders including breast cancer. The antineoplastic activity of taxol mediates interfering with mitosis through stabilization of the microtubules that make up the mitotic spindle. We hypothesized that the mitotic effect that results from inhibition of stathmin expression may synergize with the mitotic effect of taxol and result in a more profound inhibition of the malignant phenotype. We first demonstrated that exposure to taxol at low nanomolar concentrations can significantly decrease the proliferation of K562 cells in which stathmin is inhibited, but has no effect on control K562 cells in the absence of stathmin inhibition. We also showed that taxol resulted in a more profound increase in the number of multinucleated cells in the presence of stathmin inhibition. In contrast, nocadozole, which has a microtubule destabilizing activity opposite to that of taxol, has no effect on the growth of K562 cells in the presence of stathmin inhibition while it suppresses the growth of the control K562 cells. The synergy between the anti-tumor activity of stathmin inhibition and taxol was investigated in an *in vitro* clonogenic soft agar assay. Clonogenicity of K562 cells was decreased by 55% following anti-sense inhibition of stathmin and by 30% following taxol exposure. However, the combination of anti-sense and taxol resulted in a 92% decrease in clonogenicity. This suggests synergistic interaction between taxol and anti-sense inhibition of stathmin since the effect of the combination is more than the sum of the two separately. These findings in leukemic cells that are not particularly sensitive to the antineoplastic activity of taxol are promising. It is possible that the synergistic interactions may be more significant in taxol-sensitive tumors such as breast cancer. This novel therapeutic approach may become an effective form of cancer therapy that will have the added advantage of reducing the severe toxicities associated with the use of multiple chemotherapeutic agents with similar toxicity profiles.

Regulation of Early Hematopoietic Gene Expression by the HMG Domain Protein SSRP1/PREIIBF. P.J. Hayes, M.A. Dyer, and M.H. Baron. Department of Medicine, Division of Hematology, Mount Sinai School of Medicine, New York, NY.

The human embryonic β-like globin gene (epsilon) is expressed in primitive erythroid cells of the yolk sac during the first few weeks of development. We have previously shown that developmental stage-specific expression of the epsilon-globin gene is mediated hy multiple positive and negative regulatory elements upstream of the start of transcription. Of particular interest is one Positive Regulatory Element, PRE II, that works together with other elements (PRE I and PRE V) to confer developmental stage- and/or tissue-specific expression on a minimal promoter. An ~85–90 kDa PRE II binding factor (PREIIBF) was identified in the nuclei of erythroid cells and shown to bind specifically to a novel 19 bp region within PRE II; binding of this protein to PRE II resulted in bending of the target DNA and was required for promoter activation. In this report, we present the cDNA expression cloning of PREIIBF. The cDNA encodes a previously identified member of the HMG domain family of DNA binding proteins termed SSRP1. By a number of biochemical and immunological criteria, recombinant SSRP1 protein appears to be identical to the PREII binding factor from erythroid nuclei. A hallmark of HMG domain proteins is their ability to bend their target DNAs; therefore, as we speculated previously, DNA bending by SSRP1/PREIIBF may contribute to the mechanism by which PRE II synergizes with other regulatory elements located upstream and downstream. In contrast with reports from other investigators, we demonstrate that SSRP1 binds DNA with clear sequence specificity. Moreover, we show that SSRP1/PREIIBF lacks a classical activation domain but that binding by this protein to PRE II is required for activation of a minimal promoter in stable erythroid cell lines. Like the related lymphoid-enhancer factor (LEF-1), SSRP1/PREIIBF may function as a context-dependent transcription factor. These studies provide the first evidence that SSRP1 plays a role in transcriptional regulation. SSRP1/PREIIBF may serve an architectural function by helping to coordinate the assembly of a multiprotein complex required for stage-specific regulation of the human epsilon-globin gene. Although Northern blot analyses had initially suggested that SSRP1/PREIIBF is widely expressed, our more recent *in situ* hybridization experiments indicate that this is not the case, and that, in at least some cases, the apparent expression in a variety of other tissues reflects the presence of hematopoietic cells. SSRP1/PREIIBF is clearly expressed in erythroid cells in the embryo and may be restricted within a subset of embryonic hematopoietic cells. Recent work from another laboratory (C. Patterson, personal communication) has suggested the possible involvement of SSRP1/PREIIBF in regulation of the *Flk*-1 protein-receptor tyrosine kinase gene. Because *Flk*-1 is expressed in hematopoietic progenitors and because it, like the globin genes, belongs to a multigene family, we suggest that SSRP1/PREIIBF may play a role in regulation of families of genes during early hematopoietic development.

Retroviral Mediated Misexpression of p21 in Retinal Progenitor Cells Alters Differentiation *in vivo*. M.A. Dyer[1,2], M.H. Baron[1], and C. Cepko[2]. [1]Department of Medicine, Division of Hematology, Mount Sinai School of Medicine, New York, NY; and [2]Department of Genetics, Harvard Medical School, Boston, MA.

Cell cycle exit is tightly coordinated with cell-type specific gene expression in many tissues during development. However, the mechanism underlying communication between the differentiation program and the cell cycle machinery has been difficult to elucidate using existing experimental systems. To begin to explore this question in the developing rodent retina, a recombinant retroviral vector carrying the cyclin kinase inhibitor p21 and an alkaline phosphatase reporter gene was constructed and a high titer retroviral stock was generated. Individual retinal progenitor cells were infected *in vivo* by intraocular injection and the effects of p21 misexpression were assayed following complete retinal differentiation. More than 500 clones were scored for composition (cell type) and size (cell number) by serial reconstruction of clones of alkaline phosphatase expressing cells in retinal sections. Clones of cells expressing p21 were smaller indicating premature progenitor cell cycle withdrawal which is consistent with the role of p21 as a cyclin kinase inhibitor (CKI). In addition, one of the seven cell types normally found in the mature retina was completely lacking in clones expressing p21, suggesting that this protein may be playing a role in differentiation beyond simple cell cycle withdrawal. Altered clonal composition is specific to p21 as misexpression of a related family member, p57, did not give the same result. These data, in combination with the expression pattern of p21 during retinal development suggest that this protein may be a critical link between the cell cycle machinery and the differentiation program in the retina.

Induction of Mammalian Hematopoiesis and Vasculogenesis During Development. M. Belaoussoff[1], S.M. Farrington[1], K. Tangeman[2], and M.H. Baron[2]. [1]Department of Molecular and Cellular Biology, Harvard University, Boston, MA; and [2]Department of Medicine, Division of Hematology, Mount Sinai School of Medicine, New York, NY.

Hematopoiesis and vasculogenesis are generally considered to arise in the early embryonic mesoderm of the mouse during gastrulation, but the mechanisms by which these processes are initiated and restricted within the developing embryo are not well understood. We have devised a novel transgenic embryonic explant culture system to analyze the potential role of non-mesodermal signals in the induction and patterning of the earliest hematopoietic and vascular systems. Using this explant culture assay, we have demonstrated that interactions between primitive (visceral) endoderm and embryonic ectoderm are required in early gastrulation stage embryos for initiation of hematopoiesis and vasculogenesis. The requirement for primitive endoderm interactions can be substituted with conditioned medium from a visceral endoderm cell line. Moreover, trans-filter experiments clearly show that direct cell-cell interactions are not required for activation of primitive hematopoiesis by primitive endoderm. Therefore, these interactions are mediated by diffusible signals. Primitive endoderm signals are essential during a narrow window of development (pre- to mid-gastrulation). Remarkably, visceral endoderm signals can respecify anterior (nonhematopoietic) ectoderm devoid of any mesodermal cells to form blood and to activate vascular endothelial markers, and are therefore instructive. Reprogramming of the anterior developmental program does not require cell contact and appears to involve diffusible signal(s) acting transiently and at short range. These studies indicate that primitive endoderm signaling is a critical early component of the earliest hemato-vascular system in the mouse embryo and may also play a role in anterior-posterior patterning during development. More recent studies in our lab have demonstrated that signaling molecules present in primitive endoderm in the developing mouse embryo can also stimulate colony production from adult bone marrow cells in hematopoietic progenitor cell assays. The activities of these molecules is apparently not lineage-specific and may indicate that their targets may be stem/progenitor cells rather than more mature precursors. These experiments suggest the interesting possibility that embryonic hematopoiesis-activating factors may also serve a function in proliferation and possibly differentiation of stem/progenitor cells throughout development and may suggest new and more effective therapeutic approaches for hematopoietic and vascular diseases.

Reduction of Annexin-V Binding to Phospholipids in the Antiphospholipid Syndrome: A "Lupus Procoagulant" Phenomenon. J.H. Rand, X.-X. Wu, H.A.M. Andree, J.B. Alexander Ross, E. Rusinova, M.G. Gascon-Lema, C. Calandri, and P.C. Harpel. Department of Medicine, Divisions of Hematology and Thrombosis, and Department of Biochemistry, Mount Sinai School of Medicine, New York, NY.

The antiphospholipid (aPL) syndrome is a thrombophilic condition marked by antibodies that recognize anionic phospholipid-protein cofactor complexes. We recently reported (N Engl J Med 1997; 337(3):154 – 160) that aPL syndrome immunoglobulin G (IgG) fractions reduce the level of annexin-V, a phospholipid-binding anticoagulant protein, on cultured trophoblasts and endothelial cells, and accelerate coagulation of plasma exposed to these cells. We therefore investigated whether aPL antibodies might directly reduce annexin-V binding to inert phospholipid substrates. Using ellipsometry, we found that aPL IgGs reduce the quantity of annexin-V bound to PS/PC phospholipid bilayers; this reduction is dependent upon the presence of β_2-glycoprotein I. Also, exposure to plasmas containing aPL antibodies reduce annexin-V binding to phosphatidyl serine-coated microtiter plates, frozen thawed washed platelets, activated partial thromboplastin time (aPTT) reagent and prothrombin time reagent and reduce the anticoagulant effect of the annexin-V.

These studies show that antiphospholipid antibodies interfere with the binding of annexin-V to anionic phospholipid and with its anticoagulant activity. This acceleration of coagulation, due to reduced binding of annexin V, stands in marked contrast to the "lupus anticoagulant effect" previously described in these patients. These results are the first direct demonstration of the displacement of annexin-V and the consequent acceleration of coagulation on noncellular phospholipid surfaces by aPL antibodies.

Efficient Transfer and Long-Term Expression of the Human Beta-Globin Gene in an *in vivo* Murine Bone Marrow Transplantation Model. I.S. Meeus, K. Chirkova, S. Ren, H. Lung, R. Weinberg, and G. Atweh. Department of Medicine, Division of Hematology, Mount Sinai School of Medicine, New York, NY.

The use of retroviral vectors to transfer globin genes into hematopoietic stem cells has faced many different problems in the past. The earlier generations of globin retroviral vectors suffered from genetic instability, low titers and low levels of expression. We previously described a new class of gamma-globin retroviral vectors designed for the gene therapy of sickle cell disease. These retroviruses carried an enhancer element from the α-globin gene cluster (HS-40) to increase the level of expression of the linked human gamma-globin gene. These viruses are genetically stable, can be produced at high titers and can give rise to high-level expression in transduced erythroid cells. We have now generated two new retroviral vectors designed for the gene therapy of β-thalassemia. These HS-40-based vectors carry a human β-globin gene modified by deleting the recombinogenic sequences of IVS-2. Both vectors were produced in titers > 1×10^6 pfu/mL. The first vector [N2Aβ(HS-40)] is based on a retroviral backbone that includes a neo^r selectable gene. The transduction efficiency of the [N2Aβ(HS-40)] vector after G418 selection *in vitro* was high as reflected by integration of the human β-globin gene in nearly 100% of the MEL cells. However, the level of expression of the human β-globin gene *in vitro* was only 0.8% of the level of expression of the murine beta^{maj}-globin gene. Transduction of murine bone marrow followed by G418 selection and transplantation resulted in integration of the retroviral sequences in more than 50% of the circulating blood cells of the transplanted mice. Although expression was stable for more than 8 months after transplantation, the level was less than 1% of the mouse beta^{maj}-globin gene. This suggests competition between the globin promoter and the LTR promoter driving the expression of the neo^r gene. We constructed another retroviral vector [M48β(HS-40)] based on a backbone without selectable genes. The transduction efficiency of this vector *in vitro* was low, as reflected by the integration of the human β-globin gene in less than 1% of the MEL cells. *In vivo*, [M48β(HS-40)] was expressed at a high level (> 50%) but in a small minority of the red blood cells (RBCs) of transplanted mice. This data shows long-term integration and expression of the [N2Aβ(HS-40)] vector in an *in vivo* animal model. In contrast, the [M48β(HS-40)] vector results in high level expression of the human β-globin gene although transduction efficiency without G418 selection is low. Nonionic selection by Green Fluorescent Protein (GFP) under the control of different promoters within the [M48β(HS-40)] context is currently under investigation.

Cord Blood Program – Hematopoietic Stem Cell Database. D. Skerrett[1], A. Yang[2], L. Rudon[3], W. Huang[2], and C. Bonomo[2]. [1]Division of Hematology and Departments of [2]Information Management Systems and Services and [3]Blood Bank, Mount Sinai School of Medicine, New York, NY.

The development of a cord blood bank requires computer support similar to that utilized in conventional blood centers. The banking of cord blood for storage and future transplantation also presents many unique data management issues. For example, conventional blood donor criteria are utilized, but subsequent retesting of inventory and notification of donors may occur. Furthermore, the need to store and manipulate HLA data for inventory management and transplant searching, renders commercial blood banking systems unacceptable for cord blood banking. We developed an information system for the collection of data, management of inventory, interpretation of results, and performance of quality metrics specific to the cord blood program. The database is written in Microsoft Access and utilizes Visual Basic for applications. Bar-code printing for product identification and scanning is also supported. Labeling and bar-code assignments are in compliance with ISBT 128 standards for universal application of labeling for blood products. All transactions are performed utilizing unique product identifiers that are linked to the donor identity by restricted access. Data is captured in transaction fields that are specific for collection demographics, HLA antigen results, processing information, family history, high risk history, infectious disease testing results, details of processing, and inventory management. Sorting, tracking, and searching functions provide reports for assessing procedure outcome, quality control, and quality assurance for large scale processing. Donor and product processing controls, consistent with regulatory and professional standards, are built into the system with the use of field limits, edit checks, and processing ranges. Cord blood datasets are electronically transmitted for international registry access for utilization in unrelated transplantation. The development of this database allows the Mount Sinai Cord Blood Program to capture and rapidly analyze a large volume of cord blood data. The database is instrumental to the operation of the bank and the continuous quality improvement monitoring that is critical for a GMP facility. The unique requirements for cord blood data management have been met by the development of this computer system for hematopoietic stem cell processing.

Umbilical Cord Blood Banking at The Mount Sinai Medical Center. D. Skerrett[1], L. Rhone[2], A. Yang[1], R. Jiang[1], O. Rosina[1], M. Spivack[1], L. Isola[1], and S. Fruchtman[1]. [1]Division of Hematology, Department of Medicine and [2]Department of Obstetrics and Gynecology, Mount Sinai School of Medicine, New York, NY.

Umbilical cord blood (UCB) is a novel source of progenitor cells for bone marrow transplantation. The presence of an on-site collection, processing, testing, and storage facility permitted us to establish a GMP tissue bank for long-term banking of UCB. Cord blood collections began in March 1998. Potential maternal donors receive donor information in the second trimester of pregnancy. At delivery, participating donors provide a medical, genetics, and high-risk factor history, consent for HIV testing, and consent for donation. UCB is collected by a dedicated collections staff on the labor and delivery floor. *Ex utero* collections, into a closed system, begin within 10 minutes of delivery of the placenta. UCB is processed for red cell depletion, buffy coat concentration, and cryopreserved at -190° C. All UCBs are typed for HLA class I and II antigens by DNA SSP methods. The results of the first 3 months of activity are presented. Ninety-three percent of mothers donated to the cord blood bank. Some donations were not processed for banking due to medical deferral (6.9%), damaged placentas (16.0%), or other factors (22.9%). Nine mothers (0.8%) elected private bank donation. Three donors (0.7%) were deferred for positive hepatitis B serology. An additional 23 (5.3%) of UCB donations were placed in quarantine due to unconfirmed serological reactions for hepatitis B core antibody or HTLV I/II. The bacterial contamination rate at collection was 0.45%. Of 1092 deliveries during this period, 435 UCBs (39.8%) are entered into the bank. Product characteristics are described in the following table:

Collection volume	< 100 mLs	> 100 mLs
Number of UCBs	217	218
Nucleated cell count frozen (x 10^6)	458	1117
CD 34 cell count frozen (x 10^6)	4.01	9.9
CD 3 count frozen (x 10^6)	401	362
Post processing cell recovery (%)	87.5	92.5

We have established a hospital based umbilical cord blood bank for the production of progenitor cells for transplantation. All activities of the bank take place on the Mount Sinai campus. The rapid collection process and on-site processing facility result in products with high cell yields and low bacterial contamination rates. The cell doses obtained are within the ranges that are applicable for transplantation in pediatric and adult recipients.

Degradation Pathway of a Misfolded Integrin Subunit from a Patient with Glanzmann's Thrombasthenia. D.L. French, C.M. Grimaldi, C. Cardozo, E.A. Fisher, B.S. Coller, and J.C. Unkeless. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Integrins are integral membrane protein heterodimeric complexes that mediate cell-cell and cell-extracellular matrix (ECM) adhesive interactions. The a and b subunits of the integrin receptor are synthesized as single-chain precursor molecules that associate to form a complex that is transported to the cell surface. Subunits may be synthesized at different rates and in different stoichiometric amounts; therefore, mechanisms must be available to ensure that only properly assembled and stable complexes reach the cell surface. If either subunit is not expressed or if the subunits do not associate properly, the polypeptide chains are retained in the endoplasmic reticulum (ER) and eventually degraded. The exact location of the degradative system and the mechanisms involved are undefined. We are studying the platelet integrin GPIIb/IIIa receptor which is the most abundant member of the integrin family found on the platelet surface, representing ~15% of total surface protein. This receptor plays a critical role in both hemostasis and thrombosis. The involvement of GPIIb/IIIa in platelet aggregation is underscored by the fact that aggregation is absent in patients with the bleeding disorder Glanzmann's thrombasthenia. Underlying this disorder are mutations in the GPIIb or GPIIIa genes resulting in qualitative or quantitative abnormalities of the GPIIb and/or GPIIIa subunits. The mutations resulting in biosynthetic defects have been shown to affect either subunit assembly or transport of assembled complexes from the ER to the Golgi. We have identified a C374Y mutation in the GPIIIa subunit from a patient with Glanzmann's thrombasthenia. Previous studies have shown that this mutation results in ~10% of normal levels of GPIIb/IIIa receptors on the surface of the patients' platelets. Mammalian cell expression studies demonstrated that the receptors that are expressed on the cell surface are functionally normal, but in reduced numbers. Mutagenesis of both cysteine residues involved in disulfide bond formation in the normal GPIIIa subunit restored surface receptor expression to approximately 50% of normal levels. These data suggest that the presence of a free sulfhydryl group in the mutant receptor may cause misfolding of the GPIIIa subunit, thus targeting it for degradation. Stable CHO cell lines expressing normal and mutant receptors were incubated with protease inhibitors including MG132, an inhibitor of the proteasome. Only the mutant GPIIIa subunit was protected from degradation by MG132. In addition, MG132 treatment of these cells resulted in the increased expression of the heat shock protein Hsp-70, which is normally induced in response to this inhibitor. This study is the first to suggest that the proteasome may play a role in the degradation of misfolded integrin subunits.

Allogeneic Peripheral Stem Cell Transplantation for High-Risk Patients at Mount Sinai. A. Shah[1], S. Fruchtman[1], M. Zangari[1], E. Scigliano[1], B. Shank[2], D. Skerret[1], L. Isola[1]. [1]Department of Medicine, Division of Hematology, and [2]Department of Radiation Oncology, Mount Sinai School of Medicine, New York, NY.

Peripheral blood stem cells (PBSC) have virtually replaced bone marrow as a graft in autologous transplants. Concern that infusing large number of T-lymphocytes results in a high incidence of chronic graft-versus-host disease (GvHD) has deterred its widespread use in allogeneic transplantation. PBSC grafts result in more rapid hematopoietic and immune reconstitution, lower-regimen-related toxicity (RRT) and mortality (RRM),, and shorter hospitalizations. A rapid immune reconstitution is desirable in patients at high risk for disease relapse. Likewise, rapid engraftment is most important in those patients more likely to experience RRM and RRT. We performed 13 allogeneic PBSC transplants between August 1996 and April 1998. PBSC were collected from related donors after mobilization with filgrastim. For matched donors, no manipulations were performed on the PBSC. Mismatched grafts were T cell depleted by means of positive CD34$^+$ selection. Recipient age (median/range) was: 32 (4–48). There were 4 females and 8 males. All but one patient with aplastic anemia had advanced hematologic malignancies. Preparative regimens included total body irradiation (TBI) in 7 cases. Seven patients received unmanipulated and 5 CD34$^+$ selected PBSC. All patients received GvHD prophylaxis with cyclosporine and methotrexate or prednisone. Four recipients received PBSC from multiparous female donors. The other received male cells. Human leukocyte antigen (HLA) mismatching varied from two antigens to a full haplotype mismatching. The PBSC grafts contained 14x10^6 (4–51 x10^6) CD34$^+$/kg and 270x10^6 (148–350 x10^6) CD3$^+$/kg. The CD34$^+$ selected grafts contained 2x10^6 (1.3–4.6 x10^6) CD34$^+$/kg and 1.59x10^6 (0.2–2.9 x10^6) CD3$^+$/kg. Engraftment of neutrophils (ANC>500) was prompt 13 (10-NA). Seven patients achieved a platelet count >20,000 between day 13–25. The rest of the patients were not evaluable for platelet engraftment. Three patients were alive on post-BMT days 12–69. One patient had acute GvHD of the skin and 2 of the gut and liver. One patient died of severe VOD, 3 of relapsed disease, and 6 died of infectious complications and/or interstitial pneumonitis. Allogeneic PBSC provide a suitable graft for allotransplantation. The incidence of acute GvHD is modest. Early disease relapse is not eliminated with the use of PBSC. RRM and RRT (58%) were, as expected, high in this group. This data supports the continued use of PBSC allotransplantation for patients at high risk for relapse and RRT/RRM. The use on non-myeloablative regimens and more aggressive prophylactic antivirals and antifungals may render this therapy as successful as bone marrow transplantation for standard risk patients.

Structural and Functional Analysis of the PLZF POZ Repression Domain. A. Melnick, S. Arai, A. Polinger; and J. Licht. Department of Medicine and Brookdale Center of Molecular Biology, Mount Sinai School of Medicine, New York, NY.

The promyelocytic leukemia zinc finger (PLZF) protein is a transcriptional factor, highly expressed in hematopoietic progenitor cells, that may be critical for the growth and development of myeloid cells. Recent work from our lab suggests that PLZF is a growth suppressor whose activities are disrupted in patients with t(11;17) acute promyelocytic leukemia. The PLZF protein contains an N-terminal poxvirus zinc finger (POZ) motif which is also a transcriptional repression domain. Proteins that contain POZ domains can mediate transcriptional regulation and in some cases may mediate control of gene expression by modulating chromatin structure. Our broad goals are to understand how PLZF functions as a transcriptional repressor and what role the POZ domain plays in the overall effect of this protein on cell growth and development. Work from our lab has shown that the PLZF POZ is the main repression domain of PLZF and is responsible for nuclear sublocalization and homodimerization. We created a bank of 15 POZ domains with point mutations, deletions and alanine scanning. The basis for targeting the selected regions and amino acids came from computer-generated structural analysis that we performed combined with selection of residues conserved across species, phylum and different proteins containing POZ domains. We then performed the first structural function analysis ever on a repression domain and on a POZ domain. We created the above mutants using polymerase chain reaction (PCR); the resulting products were confirmed by sequencing. Using the Yeast two hybrid system, we were able to determine critical residues required for self-association of the POZ domain. We also were surprised to find that certain point mutations increased binding. Expression of the mutants was confirmed by Western Blotting and in frame expression by sequencing. We then explored the transcriptional properties of these mutants using reporter assays in human cells. The constructs were confirmed to be in frame by sequencing, and expression was confirmed by Western Blotting. Through these studies, we were able to determine residues critical for this function as well. Although there was very good correlation with self-association, to our surprise, certain areas of the molecule appeared to be dispensable for repression though not for dimerization. We were able to identify crucial helical regions required for POZ function. Furthermore, the tight binding mutants were also stronger repressors. Current studies underway include testing the impact of these mutants on PLZF-induced growth suppression and nuclear localization. We have thus described the structure-function of the PLZF POZ domain and will soon clarify how this correlates with its biological spectrum of actions.

The PLZF Leukemia Protein Interacts Functionally and Structurally with the ETO Leukemia Protein Suggesting Novel Pathways of Leukemogenesis. A. Melnick, S. Arai, H. Ball, A. Polinger, and J. Licht. Department of Medicine and Brookdale Center of Molecular Biology, Mount Sinai School of Medicine, New York, NY.

The promyelocytic leukemia zinc finger (PLZF) protein is a transcriptional factor, highly expressed in hematopoietic progenitor cells, that may be critical for the growth and development of myeloid cells. Recent work from our lab suggests that PLZF is a growth suppressor whose activities are disrupted in patients with t(11;17) acute promyelocytic leukemia. PLZF has been demonstrated to interact with a transcriptional Repression Complex which includes the nuclear receptor co-repressors N-CoR and SMRT, as well as Sin3-A. Thus PLZF can recruit histone deacetylases to its target genes and cause transcriptional repression to occur. This mechanism is likely to be the cause of retinoic acid resistance in t(11;17) APL. To further understand the function of PLZF in transcriptional repression, we are studying the transcriptional effects of these proteins together with PLZF. We also are interested in other proteins which might functionally interact with PLZF both in normal and leukemic cells. To this end, we have conducted functional studies with histone deacetylase 1, 2 and 3. Our human cell reporter assays demonstrate a functional interaction with all three of these proteins, defined by a marked potentiation of PLZF transcriptional repression. Furthermore, we have shown for the first time a functional interaction between PLZF and histone deacytelase 3 (HDAC3). In addition, we have performed yeast two hybrid experiments with N-CoR and SMRT. Interestingly, we have not been able to confirm that these interact with the POZ domain of PLZF, in contrast to the work of Dejean's group but in accordance with Pelicci's group. We recently learned that the protein 821 oncogene (ETO), involved in t(8;21) acute meyeloid leukemia (AML), also associates with the same transcriptional repression complex. ETO is fused to the AML-1 gene product, resulting in the inappropriate repression of AML-1 target genes, normally required for myeloid differentiation. For the first time, we show an interaction between ETO and PLZF, although not with the POZ domain. Binding was demonstrated using the yeast-two-hybrid system and in mammalian cell co-immunoprecipitation assays. Furthermore, we have found a functional interaction between ETO and PLZF. Using human cell reporter assays, we were able to demonstrate that ETO potentiates the repression caused by the PLZF POZ domain, PLZF itself, and more importantly, the repression effect of full-length PLZF on a natural endogenous promoter sequence. The interaction of PLZF and ETO has also been studied. In these experiments, HDACs appear to rescue the ability of high doses of PLZF and ETO to repress, whereas normally a squelching effect is seen. We have thus discovered a novel mechanism of action for PLZF and only ETO. These findings suggest a possible common pathway of leukemogenesis for several "good prognosis" subtypes of AML.

Cytotoxic Activity of Anti-Tac(Fv)-PE38 Toward Lymphocytes from Patients with Hairy Cell Leukemia. D.H. Robbins, I. Pastan, and R.J. Kreitman. Mount Sinai School of Medicine, New York, NY.

Beta 3 Integrin Knockout Mice Display a Glanzmann Thrombasthenia Phenotype. K.M. Hodivala-Dilke, K. McHugh, D.A. Tsakiris, L.E. Scudder, S. Smyth, S. Lengweiler, D. Patel, H. Vaananen, E. Reis, R. Gordon, H. Rayburn, F.P. Ross, B.S. Coller, S. Teitelbaum, and R.O. Hynes. Howard Hughes Medicine Institute, Massachusetts Institute of Technology, Cambridge, MA; Department of Pathology, Washington University School of Medicine, St. Louis, MO; and Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Preparation and Preliminary Characterization of Hamster Monoclonal Antibodies to Mouse Platelet Proteins. S. Lengweiler, L.E. Scudder, H. Park, M. Jirouskova, S. Smyth, T. Moran, and B.S. Coller. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Seroprevalence of *Helicobacter Pylori* (HP) in Patients with Non-Hodgkin's Lymphoma (NHL): Comparison with Other Hematological Disorders. J. Cuttner, S. Itzkowitz, P. McGlynn, A. Chen, C. Bodian, S. Ogata, and J.L. Werther. Departments of Medicine and Biomathematical Sciences, Mount Sinai School of Medicine, New York, NY.

Stem Cell Factor (SCF) Increases *in Vitro* Γ-globin Synthesis by Erythroid Colonies (BFU-E) from Sickle Cell Disease Patients (HbSS). R.S. Weinberg, Y. Galperin*, and M. Brokhin*. Department of Medicine, Division of Hematology, Mount Sinai School of Medicine, New York, NY.

***Ex Vivo* Expansion of Erythroid Progenitor Cells (BFU-E) from Patients with Sickle Cell Disease (HbSS).** R.S. Weinberg, and Y Galperin. Department of Medicine, Division of Hematology, Mount Sinai School of Medicine, New York, NY.

Infectious Diseases

Thalidomide for the Treatment of Esophageal Aphthous Ulcers in Patients with Human Immunodeficiency Virus Infection. J.M.

Jacobson[1], J. Spritzler[2], L. Fox[3], J.L. Fahey[4], J.B. Jackson[5], and the National Institute of Allergies and Infectious Diseases AIDS Clinical Trials Group. [1]Department of Medicine, Division of Infectious Diseases, Mount Sinai School of Medicine, New York, NY; [2]Statistical Data Analysis Center, Harvard School of Public Health, Boston, MA; [3]National Institute of Allergies and Infectious Diseases, NIH, Bethesda, MD; [4]Department of Medicine, University of California, Los Angeles, Los Angeles, CA; and [5]Department of Pathology, Johns Hopkins School of Medicine, Baltimore, MD.

Patients with advanced HIV infection can experience severe painful aphthous ulceration of the esophagus. We previously reported thalidomide to be effective in healing aphthous ulcers of the mouth and oropharynx in HIV-infected patients. We now report the results of a double-blind, randomized, placebo-controlled study of thalidomide as treatment for esophageal ulcers in HIV-infected patients. Twenty-four patients received either 200 mg of thalidomide or placebo orally once per day for 4 weeks. Eight of 11 (73%) patients in the thalidomide-randomized group had complete healing of ulcers after 4 weeks, compared to 3 of 13 (23%) patients in the placebo group (OR 13.82, 95% CI 1.16–82.75; $p = 0.033$). Adverse events included somnolence, rash, and peripheral sensory neuropathy.

Thalidomide is effective in healing HIV-associated aphthous ulceration of the esophagus.

Cost-Effectiveness of Tuberculosis Preventive Therapy for HIV-Infected People in Sub-Saharan Africa. J.C. Bell, D.N. Rose, and H.S. Sacks. AIDS Clinical Trials Unit, Mount Sinai School of Medicine, New York, NY.

Objective: To determine the effectiveness and cost-effectiveness of TB preventive therapy for HIV-infected persons in sub-Saharan Africa.

Methods: We used a Markov transition-state model, the results of randomized clinical trials of tuberculosis preventive therapy in sub-Saharan Africa, and literature-derived medical care costs to evaluate three preventive therapy regimens: (1) daily isoniazid (INH) for 6 months, (2) daily INH and rifampin (RIF) for 3 months, and (3) twice-weekly RIF and pyrazinamide (PZA) for 2 months.

Outcome measures: Life expectancy, tuberculosis cases per cohort, cost and cost per quality-adjusted life year saved. We performed the analysis using three different cost scenarios: (1) medical care costs only, (2) medical care and social (indirect) costs, and (3) medical care and social costs for both primary and secondary infections.

Results:

	Life expectancy (years)	TB cases (per 100,000)	Quality-adjusted life expectancy (years)	Cost (per person)	Cost/ QALY
No preventive therapy	7.79	38,126	3.09	$25.30	–
INH 6 months	8.37	30,020	3.20	$38.31	$114
INH + RIF 3 months	8.31	30,913	3.19	$53.29	$275
RIF + PZA 2 months	8.43	29,246	3.21	$57.85	$260

This table reports the outcome values calculated by the model for the three preventive therapy regimens and for no preventive therapy. The costs include only medical care costs. When social costs are included, the cost for no preventive therapy exceeds the cost of INH for 6 months ($87 vs $75 per person); when social costs and the cost of treating secondary infections are included, all three regimens are less expensive than preventive therapy. In this last scenario, INH for 6 months yields a per person savings of $24.16.

Conclusions: TB preventive therapy results in monetary savings over the case-finding and treatment strategy currently in use in sub-Saharan Africa. We recommend that tuberculosis policy in sub-Saharan Africa be changed to include preventive therapy for HIV-infected tuberculin reactors.

Cure of Disseminated Tuberculosis with Non-conventional Regimens in Orthotopic Liver Transplant Patients. B.R. Meyers[1], G.A. Papanicolaou[1], P. Sheiner[2], S. Emre[2], and C. Miller[2]. [2]Department of Medicine, Division of Infectious Diseases and [2]Recanti-Miller Transplant Institute, Mount Sinai School of Medicine, New York, NY.

Background: Since increased hepatotoxicity was observed with first line anti-tuberculous agents using 4- drug standard induction therapy in orthotopic liver transplant patients, we evaluated the efficacy and adverse effects of a novel continuation regimen for the treatment of tuberculosis in orthotopic liver transplant patients at a university hospital in New York City.

Methods: The hospital records of all patients who were referred to Mount Sinai Hospital (n = 924) and who underwent orthotopic liver transplant between September 1988 and May 1998 were reviewed. Data was collected from patient records. Nine orthotopic liver transplant patients (0.97%) developed tuberculosis over a 9.5-year period. Seven of 9 (78%) patients had disseminated tuberculosis including 2 patients with meningitis.

All mycobacterial isolates were sensitive to isoniazid, rifampin, pyrazinamide and ethambutol. Standard induction therapy with 3 or 4 drugs was given for 2 months (mean). Hepatotoxicity related to the standard induction regimen developed in 7/8 (87.5%) patients. Liver biopsy during induction therapy revealed drug-induced hepatitis in 5/6 (88%) patients and rejection in 6/6 (100%) patients. Continuation regimens consisted mainly of ethambutol and ofloxacin; mean length of therapy was 9 months.

Results: Overall mortality was 33.3% (3/9 patients) over a 4.5 year follow-up period. Tuberculosis-associated mortality was 22.2%. One patient died prior to therapy, and another died with concomitant bacterial sepsis during induction therapy. Six of 7 patients are alive and disease free. One patient died of recurrent hepatitis C and graft failure without evidence of tuberculous infection at death. Another, retransplanted for hepatic rejection, remains disease free at one year. The mean follow-up for 6 patients that completed treatment was 3.75 years (2.5–5.3 years). Six are free of tuberculosis.

Conclusions: Our experience reveals that orthotopic liver transplant patients have poor tolerance for conventional therapy due to the inherent toxicity of these agents and their concomitant bouts of organ rejection. Our non-conventional therapy yielded remarkably good results in that 6 patients, all with disseminated disease, were well after a mean 3.5 years of follow-up. Consideration should be given to this novel follow-up therapy in patients without cavitary pulmonary disease who develop hepatotoxicity during induction.

Internal Medicine

Are In-Hospital Patients Adequately Screened for Alcoholism? V.M. Bautista, and M.P. Schori. Department of Medicine, Englewood Hospital and Medical Center, Englewood, NJ.

The aim of the study was to find out if medical residents routinely screen their in-hospital patients for alcoholism using the recommended alcohol-screening protocol. Data was collected from chart review of patients admitted to the teaching service in the General Medicine floors in a community hospital during the entire month of April 1998. Residents' admission histories and physical examinations were reviewed by one investigator. The adequacy of alcohol screening done by the residents was judged based on whether the protocol was followed. Results have shown that in-hospital patients were asked about alcohol use 87% (post-graduate year [PGY] I = 84%, PGY II = 90%) of the time, however, adequate history taking was found in only 61% (PGY I = 60%, PGY II = 62%). Using the Chi-square analysis, in-hospital patients were not adequately screened by PGY I (X2 = 0.002, df = 1, $0.950 < p < 0.975$), and PGY II (X2 = 0.728, df = 1, $0.30 < p < 0.40$). Comparison of adequate history taking by both PGY I and PGY II in both Dean 5 (X2 = 0.48, df = 1, $0.40 < p < 0.50$) and Dean 7 (X2 = 0.06, df = 1, $p = 0.80$) showed no statistical difference. Compared with previous studies, this paper had shown a higher rate of alcohol-history taking by physicians on their in-hospital patients.

However, only slightly greater than 60% of the alcohol histories reviewed were adequate based on the recommended alcohol-screening protocol.

Mammography Utilization at Medical Primary Care Clinic, Elmhurst Hospital Center. S. Abbassey, and A. Sheikh. Department of Ambulatory Care and Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Mammography is a very effective tool in the early detection of breast cancer, but there is controversy about the age groups for which it is indicated. Various governmental, professional and voluntary agencies have issued guidelines and there is general agreement on screening women aged 50–69. Screening women 40–49 is currently advocated by the National Cancer Institute, the American Cancer Society and several specialty organizations, but not by the U.S. Preventive Services Task Force (USPSTF). A study was undertaken in the Medical Primary Care Clinic (MPC) at Elmhurst Hospital Center to determine indications for and outcome of screening mammography, and to compare utilization to the recommendations by different organizations. A systematic random sample of 100 patients from the MPC clinic who were referred for screening or diagnostic mammography over a period of two months (September 1997 – November 1997) was selected. Information was gathered from the Radiology Department logbook, hospital information system (HIS) computer system and the patient's medical record. Variables recorded included: age, race, referrals by residents versus attendings, referrals by male versus female provider, body weight, family history of breast cancer, previous mammograms, hormonal replacement therapy (HRT), menopausal status, and breast clinic referrals.

- 2 (2%) of mammographies were performed in women < 40 years of age.
- 26 (26%) were performed in women 40–49.
- 53 (53%) were performed in women 50–69.
- 19 (19%) were performed in women ≥ 70.
- 70 (70%) were postmenopausal; of these 4 (5.7%) were taking HRT.

Family history of breast cancer was not recorded in 46% of charts; further study is needed to determine if omission of history taking or not recording pertinent negative history is occurring. This study suggests that mammographies ordered reflect agreement with NCI guidelines (not USPSTF guidelines). In addition, further study is warranted to elucidate the low rate of HRT at MPC.

Acute Uncomplicated Cystitis in Young Women: An Analysis of Office-Based Management Strategies at Elmhurst Hospital Center. R. Go, and A. Lyman. Department of Ambulatory Care and Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Most cases of urinary tract infections occur in young women who have acute uncomplicated cystitis. Various management strategies have been proposed regarding diagnostic procedures, choice of antibiotic and duration of treatment but consensus has not been reached. Costs for different management strategies vary widely. A retrospective cohort study was conducted, utilizing a sample of 54 patients, presenting for the first time in the clinics or ER of Elmhurst Hospital Center (EHC), who fit the criteria of having acute uncomplicated cystitis. Their charts were reviewed and pertinent data including the age, race, clinic where the patient was first managed, the diagnostic utilities used, the antibiotic of choice by the treating physician and duration of treatment were recorded. Complications of disease or therapy were sought. These strategies were then compared to the recommendations by Stamm and others (1 – 3) in the management of uncomplicated cystitis in adults. Total cost of diagnostic evaluation and therapy were computed based on the unit costs provided by EHC laboratory and pharmacy. A majority of the patients were treated in the ER or Medical Primary Care Clinic (MPC). Three (56%) were treated based on symptoms alone. Most physicians sent the urine for analysis to help them diagnose acute cystitis. Most ER doctors gave a 5-day course of cephalexin for treatment while MPC physicians ordered trimethoprim and sulfa methazole double strength (TMP/SMX DS) for 7 – 10 days. A total cost of $3,779.46 was spent to manage acute cystitis in 54 patients. No pyelonephritis or other complications were observed. There is over-utilization of urine cultures leading to unnecessary cost. EHC physicians could have reduced the cost of treatment of urinary tract infections (UTIs) if they treated their patients with 3-day course of TMP/SMX DS. In view of this, there is an ongoing effort to implement a cost-effective guideline for the treatment of acute uncomplicated cystitis in ambulatory women in the primary care and ER services at EHC.

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The Development of a Community-Based Clinical Experience in a Primary Care Internal Medicine Training Program: 1998. L.M. Reich, and R.A. David. Department of Ambulatory Care and Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Clinical experience in a community-based practice setting is of central importance in a primary care training program. It offers opportunities for clinical learning that are not readily available in other settings, with a patient population that is recognized as being not equivalent to that encountered in hospital-based inpatient or outpatient settings. The Primary Care Internal Medicine Residency Program at Elmhurst Hospital, established in 1979, has until now included continuity experience only in a hospital-based medical clinic. We describe here the development and incorporation of a community-based continuity experience into our clinical curriculum. This experience consists of three parts: (1) a community-based geriatrics practice; (2) a mobile van outreach facility providing care to a local immigrant community; and (3) the opportunity to accompany nurses on initial and follow-up home care visits. In all three settings, preceptorship is provided by full-time faculty of the Department of Ambulatory Care. The clinical experience emphasizes those principles of primary care which are best taught in a community-based setting: continuity, comprehensiveness, interdisciplinary team coordination, population-based health care, an orientation toward prevention and patient education and a recognition of the importance of the patient's environment in health and illness. The first phase of the project consisted of piloting the curriculum with a small group of housestaff who provided feedback and assisted in further refinement and development of the curriculum. In the second phase, we are assessing the performance of the new curriculum in terms of learner-centered, teacher-centered, and patient-care outcomes.

Outcome of Cholesterol Treatment with HMGCoA Reductase Inhibitors at Elmhurst Hospital Center. E.M. Magcalas, and A. Lyman. Department of Ambulatory Care and Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

The National Cholesterol Education Expert Panel (NCEP) developed guidelines in 1996 for detection, evaluation, and treatment of hyperlipidemia in adults and has recommended goals for low-density lipoprotein cholesterol (LDL-c) levels based on the number of risk factors for coronary heart disease. In 1996, Marcelino and Feingold (1) examined whether patients on monotherapy with hepatic hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors were adequately treated as per NCEP guidelines; only 33% reached the target LDL-c and less than half were monitored for hepatoxicity. A historical cohort study was conducted at Elmhurst Hospital Center (EHC) to evaluate whether patients treated with statins met LDL-c goals, and to determine whether patients were monitored for toxicity. From a computer-generated list of 500 patients who had filled their prescription for fluvastatin or pravastatin at the EHC pharmacy from May 1996 – March 1997, a systematic random sample was selected; from this, 36 patients met the inclusion criteria and were included in the study. Data on medical and treatment history, laboratory tests, and medication refill practice were obtained from medical charts, and pharmacy and laboratory databases. Fifty-eight percent of patients were followed in Medical Primary Care clinic, 25% in endocrine clinic, and 17% in cardiology clinic. All 100% received statin monotherapy for > one year. No patient had missed filling more than one month of prescriptions. Fifth-eight percent of patients were being treated as secondary prevention. Five (14%) of the patients met their LDL-c goals as recommended by the NCEP (compared to 33% in the above study [1]). Only 11% of secondary prevention patients met the goal. Even if NCEP-recommended goals were reduced by 20% (goal LDL < 120 mg/dL), 58% were still inadequately treated. Sixty-six percent of patients remain on maximal doses of pravachol. Of the 5 patients who met their goal, 4 were on maximal doses of pravachol and 1 was on twice the maximal dose. Thirty-six (100%) of patients had annual lipid and liver function tests, as compared to < 50% in the Marcelino and Feingold study (1). Further studies are recommended to investigate reasons for inadequate treatment of hypercholesterolemia at EHC.

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Characteristics of Smokers in Medical Primary Care Clinic at Elmhurst Hospital Center. E. del Rosario, and A. Lyman. Department of Ambulatory Care and Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

During the past 30 years, public health efforts have been directed toward reducing the prevalence of smoking in the United States. The American public has been surveyed repeatedly to determine smoking patterns. Although these efforts have been somewhat successful, as indicated by the steady decline in overall smoking prevalence, rates have varied among sociodemographic subgroups. Differences in smoking by gender, race, educational and socioeconomic level have been noted. Data on smoking behavior among minority groups are not as extensive as those for the general population, especially for new immigrants. Without such information, it is difficult to target, plan, and implement successful smoking interventions. Therefore, a questionnaire on smoking behavior and demographic variables was administered to a convenience sample of Medical Primary Care Clinic patients at Elmhurst Hospital Center by a single interviewer from November 1997 – April 1998. Respondents were assured of confidentiality. Smoking status for the largest subgroups was: of 27 Hispanic males surveyed, 8 (29.6%) had never smoked, 15 (55.6%) were former smokers, and 4 (14.8%) were current smokers; of 50 Hispanic females, 40 (80%) had never smoked, 7 (14%) were former smokers, and 3 (6%) were present smokers. Of 14 Asian males, 6 (42%) were never been smokers, 5 (35%) were former smokers and 3 (21.4%) were current smokers. In these subgroups, males were significantly more likely to have ever smoked (OR = 8.2, 95% CI = 3.05, 22.53, Chi-square = 23.22, $p = 0.0000014$, using EpiInfo). The proportions of ever-smokers who are currently smoking were compared for gender/racial subgroups. For Hispanic males and females, the proportions were 22% and 30% respectively; for Asians, 37% and 100%. (Corresponding proportions for whites and African-Americans were 66%, 25% and 100%, 33%). Mean number of cigarettes smoked per day was higher for males than females among Hispanics and Asians. Of 25 former smokers giving reasons for cessation, 24 (96%) cited various health reasons, 1 (4%) cited religious reasons, but none cited cost of smoking. Differences by gender were found in age at initiation and daily consumption. In this survey (as in the literature on Asia), Asian women have much lower rates of smoking than Asian males (15% vs 57%); however, with Westernization, rates are increasing, especially among career/working women. A recent survey by the CDC Office on Smoking and Health of 436 state and local prevention and cessation programs found only two studies geared toward ethnic subpopulations. Research with ethnic subgroups, including immigrants, should continue.

Evaluation of PPD Status in Englewood Hospital and Medical Center Employees over the Period of Five Years (January 1993 – December 1997). F. Hamwi, and F. Relkin. Department of Medicine, Englewood Hospital and Medical Center, Englewood, NJ.

Objective: To determine the prevalence of a positive purified protein derivative (PPD) on pre-employment testing and to assess the incidence rate of PPD conversion on annual follow-up examination in Englewood Hospital and Medical Center over the period from January 1993 – December 1997.

Methods: Charts of Employees tested PPD+ were reviewed by Employee Health staff and data was provided to me; "confidentiality of employees were maintained." Subjects characteristics were studied for: age, birth place, previous history of bacille Calmette-Guérin (BCG) vaccination, type of work, and the step of PPD+.

Results: A yearly average of 181 employees had pre-employment PPD testing, out of which 15 (8.2%) had a positive test; and those subjects studied were more likely to be younger than 35 year (56.1%), be non-U.S. born (87.9%), had no previous history of BCG vaccination (69.7%), and to be positive in the first step (71.2%). Subjects who became positive in the first step and who became positive in the second step were more likely to be younger than 35, had no previous history of BCG vaccination, and be non-U.S. born.

A yearly average of 1,366 employees were tested for annual conversion, out of which 7(0.5%) were converters; those converters were more likely to be involved in direct patient care (60.9%), but there were no significant differences in regard to age and to birth place.

Conclusion: About 8% of new employees tested PPD+ on pre-employment testing and they were more likely to be younger, foreign born, and have no history of BCG vaccination. About 0.5% of employees who had annual testing were converters, and there was a trend in this group to be more likely to be involved in direct patient care.

Modifiable Risk Factors for Amputation in Diabetics. G. Robert. Department of Ambulatory Care and Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Approximately 55,000 lower extremity amputations are performed each year on diabetic patients in the United States, approximately half of the total number of non-traumatic amputations. Amputation is the end result of a cascade of diabetic lower extremity lesions due in part to lack of medical care and poor control of diabetes. The aim of this study is to evaluate the clinical characteristics and care received in patients who underwent amputation at Elmhurst Hospital Center. Similar parameters are considered in a group of diabetic patients without amputation from the Medical Primary Care Clinic (MPC). All amputations performed in an 18-month period were reviewed, and those patients with a history of diabetes were selected. A convenience sample of 23 diabetic patients currently being followed at MPC were also reviewed. Data from a retrospective chart review included demographic, clinical, and medical care characteristics. Of 37 amputations, 23 (62%) were performed in diabetics. Of these, the largest proportion were Hispanic. Of the amputees, 17.4% had had diabetes for 10–19 years, 17.4% had had diabetes for 20–29 years, 13.2% had had diabetes for 30–39 years, and in 52% duration was not recorded. In the clinic group, 78.2% of patients had had diabetes for < 10 years. The proportions with comorbid hypertension in the amputation and clinic groups were identical. In the amputation group, 30.5% of patients had denied ever smoking, 17.4% were former smokers, and 8.6% were current smokers; smoking status was not recorded in the chart for the remainder. In the clinic group, 47.8% denied ever-smoking, 17.4% were former smokers, 4.3% are current smokers, and smoking status was unrecorded in 21.7%. In the amputation group, only 17% had had a prior podiatry visit, 26% had seen the dietician, 8.6% had had a visit with the diabetes educator, and none had any record of home glucose monitoring having been performed. In the clinic group, in contrast, 26% had seen a podiatrist, 65% had seen the dietician, 26% had seen the diabetes educator, and 17.5% had had a record of home glucose monitoring. Insurance status for the amputation group was: 48% — uninsured, 35% — Medicare, 17% — Medicaid/Medicare; for the clinic group: 26% — uninsured, 21% — Medicare, and 52.2% — Medicaid/Medicare. A higher proportion of the amputation group was uninsured; a perceived lack of access to care may have contributed to the outcome. Higher proportions of the clinic patients had received ancillary services, timely referrals, and attempts to tightly control blood sugar.

A multidisciplinary team approach to preventive services (such as that utilized in MPC) may help reduce the rate of diabetic amputations in the future. As many patients with amputations presented to this institution with irreversible disease, community outreach and screening efforts are suggested in order to avoid the peripheral and autonomic neuropathy, and peripheral arterial disease which lead eventually to amputation.

Lipid Profile in Patients from the Indian Subcontinent. C. Parikh, and A. Lyman. Department of Ambulatory Care and Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

Background: The incidence of coronary artery disease (CAD) in urban India is almost equal to that of the western world. Many studies done in several countries showed that the immigrant South Asian population has abnormalities in lipid profile and a much higher incidence of CAD as compared to the native-born population.

Methods: Lipid profiles and cardiac risk factors of Indian/Pakistani, Bangladeshi and Caribbean patients of Indian ancestry (CPIA) coming to the Medical Primary Care Clinic, at Elmhurst Hospital Center were examined and compared with data on the U.S. and rural Indian population.

Results: Compared to the white U.S. males (mean cholesterol level 211 mg/dL), male patients from India, Bangladesh and CPIA had mean cholesterol levels of 222, 197 and 234 mg/dL respectively. Compared to white U.S. females (mean cholesterol 215 mg/dL), Indian, Bangladeshi and CPIA females had mean cholesterol levels of 190, 228 and 257 mg/dL. The mean low-density lipoprotein (LDL) level was higher in CPIA males (155 mg/dL) than in white, Indian and Bangladeshi males (140, 145 and 146 mg/dL respectively). The mean LDL level was similar (141 and 143 mg/dL) in white and Bangladeshi females, significantly higher in CPIA females (170 mg/dL) and significantly lower in Indian females (108 mg/dL). A cholesterol level of > 240 mg/dL was seen in 63% of Caribbean, 30% of Indian and 21% of Bangladeshi patients as compared to only 8% of healthy rural Indians. LDL level of > 160 mg/dL was seen in 10% of Indian, 31.6% of Bangladeshi and 54.5% of CPIA patients as compared to 6.7% of healthy rural Indians. The triglyceride level of > 400 mg/dL was seen in 5% of Indian, 6% of Bangladeshi and 0% of the CPIA patients as compared to 0.7% of healthy rural Indians. The high-density lipoprotein (HDL) level of < 35 mg/dL was seen in 30% of Indian, 47.4% of Bangladeshi and 9% of CPIA patients as compared to 29.7% of healthy rural Indians. When the lipid profile of South Asian patients (Indian and Bangladeshi) was compared with the CPIA, a statistically significant difference was seen in the cholesterol and the LDL levels. For the cholesterol level (< 200 vs > 200 mg/dL) the odds ratio (OR) 9.50; 95% confidence interval (CI), 1.05–217.70, p = 0.03 (Fisher's Exact Test). For the LDL level (> 130 vs < 130 mg/dL) OR, 10.53; 95% CI, 1.15–241.27, p = 0.02 (Fisher's Exact Test).

Conclusion: The CPIA had significantly higher cholesterol and LDL levels, while low HDL was seen in Indian and Bangladeshi patients. As compared to the healthy rural Indians, the immigrant Indian population had higher cholesterol, LDL and triglyceride levels while the HDL level were similar. A larger study is needed to confirm these findings and to investigate the associated environmental and the dietary factors.

Screening for Thyroid Dysfunction in the Elderly. A. Thummala, and A. Vardag. Department of Ambulatory Care and Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center (EHC), Elmhurst, NY.

Thyroid dysfunction is commonly seen in the elderly population. Subclinical hypothyroidism is associated with significant morbidity, i.e., lipid abnormalities and depression, whereas subclinical hyperthyroidism is associated with atrial fibrillation. To study the occurrence of abnormal thyroid-stimulating hormone (TSH) in the elderly population (≥ 55 years), a cross-sectional study was conducted in the Medical Primary Care Clinic at EHC. A convenience sample of 124 patients seen in the clinic by two internal medicine residents was selected and if a TSH was ordered for screening purposes; the patients were included in the sample. Among the 124 patients, 14 were found to have abnormal TSH levels (12% in females and 9% in males). Subclinical hypothyroidism was diagnosed in 8 subjects (6.4%); an additional 5 cases (4.03%) were found to be symptomatic with hypothyroidism on further investigation, and 1 (0.8%) had hyperthyroidism. The highest prevalence in the sample was seen among Asians and Hispanics. Among the Hispanics, 10.6% were found to have abnormal TSH levels, and among the Asians 20.8% had abnormal values. A higher prevalence of thyroid dysfunction has been found among Asians in some studies (1, 2). In our study, Hispanics were also found to have a high prevalence; further studies are needed to confirm this as our sample may not be representative. Unrecognized disease in these groups may represent subclinical disease or there may be difficulties in diagnosis because of language or cultural barriers. A substantial number of patients in a primary care practice who were otherwise judged asymptomatic had thyroid dysfunction with routine screening. The serum TSH may be a reliable indicator of thyroid dysfunction in the elderly.

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Adult Community Acquired Pneumonia in a Community Hospital January 1997 – June 1997. A Retrospective Analysis of 64 Cases at Englewood Hospital and Medical Center (EHMC). A. Jalloul, and M. Schori. Department of Internal Medicine, Englewood Hospital and Medical Center, Englewood, NJ.

Objective: To review clinical and laboratory findings of adult patients admitted to EHMC from January 1997 – June 1997 with diagnosis of Community-Acquired Pneumonia (CAP). To determine characteristics of presenting symptoms, mortality rate by severity of pneumonia, trends of initial antibiotic regimens used.

Methods: Retrospective chart review of 64 adult patients admitted to EHMC with diagnosis of CAP who had sputum submitted for culture was done. Patients were retrieved using the laboratory logbook for sputum culture.

Results: In all age groups, the mortality rate in severe CAP patients was 34.6%, much higher than that in the non-severe CAP patients, which was only 2.6%. The severe CAP patients constituted 40.6% of the total number of patients in the study; the remainder (59.4%) were non-severe CAP patients. Malignancy carried the highest mortality rate (40%) followed by AIDS and diabetes (33.3%) each, CAD (18.2%), immunosuppression non-HIV (16.7%), and chronic obstructive pulmonary disease (COPD) (12.5%).

The most common presenting symptom in severe CAP patients was shortness of breath (69.2%), whereas fever was seen in only 38.5% of severe CAP patients. In the non-severe CAP patients, cough was the most common presenting symptom (92.1%) and fever was seen in 52.6% of the patients as part of initial presentation.

There was a total of 11 cases of *P. Aureginosa* recovered from sputum in the patients reviewed, 6 cases in non-severe and 5 cases in severe CAP patients. Those patients with *P. Aureginosa* had COPD, Interstitial Lung Diseases (ILD) and chronic illnesses as comorbid conditions.

There was a high rate of compliance with American Thoracic Society (ATS) guidelines for empiric initial antibiotic regimen in non-severe CAP patients (86.4%) whereas only 3.8% of severe CAP patients had their initial antibiotic regimen in accordance with the ATS guidelines. The low rate of compliance in the severe group was due to lack of antipseudomonal coverage in the initial antibiotic regimens used. The average length of stay was 13.2 days and the range was 3–42 days. Those with severe CAP had higher length of stay.

Conclusion: CAP remains a serious illness with significant mortality, especially in patients who have severe presentations. The use of the ATS guidelines in stratifying patients into severe and non-severe appears to be reasonable in predicting mortality. Adherence to the ATS guidelines as far as initial empiric antibiotic regimens used should be emphasized especially for those with severe presentation. We tend to emphasize the current CDC guidelines for pneumoccocal diseases prevention by the use of the polyvalent pneumoccocal polysaccharide vaccine.

Tuberculin Skin Test Conversion in Health-Care Workers at Elmhurst Hospital Center (EHC). A. Bayoumi. Department of Ambulatory Care and Primary Care Internal Medicine Residency Program, Elmhurst Hospital Center, Elmhurst, NY.

A resurgence of TB in the United States, due in part to a confluence of homelessness, HIV infection, drug abuse, and immigration from high-prevalence areas occurred in the past decade. Even though the rate of active TB has recently decreased, hospital staff in New York City may be at relatively higher risk of occupational exposure compared to lower-prevalence areas. The prevalence of TB in physicians is greater than that found in the age-adjusted general population. Therefore, a study was conducted at EHC to assess the prevalence of known positive purified protein derivatives (PPDs) and the incidence of skin test conversions among employees at EHC by occupational group. During the study period, which was May 1995 – October 1997, 220 patients with pulmonary tuberculosis were admitted to EHC which employees about 5,000 persons. We obtained tuberculosis screening data for EHC employees from the Employees' Health Service (EHS) which administers a tuberculin skin test at the time of employment and yearly (every 6 months for those employees who are considered to be at higher risk of exposure). Skin-test conversion was defined as a positive tuberculin test proceeded by at least one negative skin test; two-step testing was done. Two hundred twenty-four physicians (44%) and 634 nurses (62%) had previously had a positive tuberculin test. Eleven of the physicians (3.8%) and 39 of the nurses (9.9%) had a documented conversion during the study period. In comparison, among clerks (a group that may have had relatively less intense contact with patients), 345 (38%) had previously had a positive test, and 19 (3.1%) had a conversion during the study period. There was a statistically significant risk of skin test conversion for physicians/nurses vs clerks (OR = 2.18, 95% CI = (1.23, 3.88), Chi-square = 8.22, p = 0.004). The recently proposed OSHA TB Standard would mandate screening every 6 months for workers at risk of exposure; we recommend continuing aggressive measures toward those employees not compliant with screening so that proposed mandates are followed. Further studies are needed to pinpoint possible occupational or geographic subgroups for whom exposure control may be suboptimal. In addition, the results of this study reinforce the importance of periodic mandatory education of all employees about their risk of contracting TB, methods of prevention, and the critical role of screening for both surveillance and disease prevention.

Recognition of Obesity as a Significant Medical Diagnosis by Internal Medicine Residents. Lori Edelman. Mount Sinai School of Medicine, New York, NY.

Liver Diseases

Zf9, a Novel Transcriptional Regulator of Urokinase-Type Plasminogen Activator in Endothelial Cells - Implications for Hepatic and Vascular Injury. S.L. Friedman[1], S. Hayashi[2], Y. Suzuki[2], and S. Kojima[2]. [1]Division of Liver Diseases, Mount Sinai School of Medicine, New York, NY; and [2]Laboratory of Molecular Sciences, Riken, Japan.

Understanding the regulation of genes controlling matrix production and degradation is essential for elucidating the basis of tissue repair. We have recently described a novel immediate-early zinc finger cDNA, Zf9, which is up-regulated in acute liver injury in hepatic stellate cells. Zf9 is also expressed in the other cellular elements of liver including endothelium, and in all mammalian tissues, suggesting a role in regulating gene expression in a variety of cellular contexts.

Aim: To study the potential regulatory role of Zf9 in urokinase-type plasminogen activator (uPA) production by endothelial cells.

Results: Zf9 is expressed by bovine aortic endothelial cells (BAECs) in response to serum or phorbol ester, and in turn transcriptionally activates uPA, a fibrinolytic factor involved in wound healing through its activation of latent transforming growth factor-β (TGF-β). Recombinant Zf9-GST (glutathione S-transferase) binds to a wild-type but not mutated guanine cytosine (GC) box motifs within the human uPA promoter (-68 to -27), with greatest affinity to the middle GC box. Transient transfection of Zf9 drives expression of a full-length uPA promoter-reporter both in BAECs as well as *Drosophila* S2 cells, which lack Zf9 and other Kruppel-like factors. Cotransfection of Zf9 with Sp1, a ubiquitous transcription factor, synergistically activates transcription. Physical interaction of recombinant Sp1 and Zf9 was demonstrated *in vitro* using affinity chromatography/Western blot. Most importantly, transiently transfected Zf9 up-regulates endogenous uPA mRNA and activity in BAECs, resulting in increased bioactive TGF-β.

Summary: Zf9, a novel transcription factor, drives uPA production and functionally synergizes with Sp1 through direct physical interaction. Activation of latent TGF-β represents a novel fibrogenic pathway of Zf9, and is the first evidence for up-regulation of an endogenous cellular activity by this transcription factor.

Cryoablation of Metastatic Neuro-Endocrine Liver Tumors: A Novel **Approach.** R. Kim, M. Shafir[2], R. Warner, and M. Sung[2]. [1]Department of Medicine, Elmhurst Hospital Center; and [2]Department of Medicine, Division of Neoplastic Diseases, Mount Sinai School of Medicine, New York, NY.

Neuroendocrine malignant tumors often metastasize to the liver causing systemic symptoms due to circulation of vasoactive substances. Surgical debulking with chemoembolization and systemic chemotherapy are the accepted treatments. Cryodestruction was investigated as a major debulking technique in 14 patients with advanced non-resectable metastases. Age range: 28–76; 12 females, 2 males.

Diagnosis: Patients were: 10 carcinoids, 2 gastrinomas, and 2 islet cell pancreatic cancers. Cryoablation of major tumors utilizing closed-circuit liquid nitrogen with total freezing never exceeding 50% of total liver volume was performed, attaining temperatures of -196°C at the tip of the probe and -40° to -80°C at the periphery of each tumor. Marked elevation of tumor serum and urinary markers after cryodestruction occurred in all patients witnessing the efficacy of this technique. There were no operative mortalities. Octreotide (Sandostatin) was used peri-operatively in all patients. One patient with gastrinoma developed disseminated intravascular coagulation requiring re-operation for bleeding. Nine patients had post-operative chemotherapy and octreotide. Mean follow-up of 23 months (range: 2–51 months); 4 patients died of progressive disease at 2, 8, 10, and 37 months, respectively; 1 patient died of unrelated disease at 1 year; and 1 was lost to follow-up. Eight patients are alive without evidence of progressive disease, on chemotherapy and Sandostatin.

Conclusion: Cryodestruction of unresectable multiple metastases of functional neuroendocrine tumors appear to be a novel safe and effective therapeutic approach. Further combined modalities studies are warranted.

Mitochondrial Aspartate Aminotransferase (mAspAT) Reaches The Plasma Membrane and is Exported from HuH7 Cells via the Golgi/Endoplasmic Reticulum. P.D. Berk[1], L. Delavega[2], and R.J. Stockert[2]. [1]Division of Liver Disease, Mount Sinai School of Medicine, New York, NY; and [2]Liver Center, Albert Einstein College of Medicine, Bronx, NY.

Besides mitochondria, mitochondrial aspartate aminotransferase (mAspAT) also occurs on plasma membranes (PMs), where it mediates fatty acid uptake. To elucidate its intracellular sorting, HuH7 cells were incubated with $[^{35}S]$-cysteine/methionine. After cell surface biotinylation, surface and intracellular proteins were separated with avidin beads. mAspAT in both cell fractions and in media was immunoprecipitated with anti-mAspAT and analyzed by sodium dodecyl sulfate-polyacylamide gel electrophoresis (SDS-PAGE)/fluorography. When chases of 0–240 min were studied following a 10 min pulse, both PM- and intracellular mAspAT were highly labeled in the 0-time chase sample, indicating rapid transfer of mAspAT to the PM. Labeled mAspAT was found in the medium by 5 min of chase. Cells were also labeled for 150 min in the presence/absence of nonactin (NA), which blocks mitochondrial protein import. In NA-treated cells, only the higher molecular weight pre-mAspAT was found in both PM and intracellular protein fractions. Hence, while the extra-mitochondrial portions of the pathway to the PM do not contain an endopeptidase that removes the "mitochondrial" presequence, excision of the presequence is not required for PM sorting. In cells incubated with either NA, brefeldin A (BrA), which collapses the Golgi/endoplasmic reticulum (ER), or with NA + BrA, BrA blocked sorting of both mAspAT and pre-mAspAT to the PM and their export into the medium.

Conclusions: mAspAT reaches the PM and is exported into the medium by a pathway involving the Golgi/ER. Since both mAspAT and pre-mAspAT reach the PM, the signal for import into this secretory pathway resides within the mature mAspAT molecule. Furthermore, since only pre-mAspAT is found on the PM in NA-treated cells, the secretory pathway does not contain an endopeptidase that excises the mitochondrial presequence. The pathway by which mAspAT normally reaches the PM must involve prior mitochondrial import for excision of the pre-sequence.

Green Fluorescent Protein-Tagged Mitochondrial Aspartate Aminotransferase Illustrates the Intracellular Sorting of the Native Enzyme. M.W. Bradbury[1], L. Delavega[2], RJ. Stockert[2], and P.D. Berk[1]. [1]Division of Liver Disease, Department of Medicine, and [2]Department of Biochemistry, Mount Sinai School of Medicine, New York, NY; and [3]Liver Center, Albert Einstein College of Medicine, Bronx, NY.

Green fluorescent protein (GFP), a 27 kDa polypeptide from jellyfish, exhibits intense fluorescence when excited by 490 nm light. Mitochondrial aspartate aminotransferase (mAspAT), in addition to its mitochondrial location, is also found on the plasma membrane (PM) of certain cells, including hepatocytes, where it mediates cellular free fatty acid uptake. The route by which mAspAT reaches the PM is unclear. Accordingly, a barium meal (Bam HI) site was introduced in plasmid pMAAT2 at the stop codon of the mAspAT coding sequence, which is downstream of a metallothionein (MT) promoter. The MT-mAspAT region was excised as an Eco-R1/BamH1 fragment, and cloned into pEGFP-1 digested with the same enzymes. This placed a genetically-engineered GFP coding sequence immediately 3' to that of mAspAT in a new plasmid, designated pMT-AAT/GFP, which also contained a *neo* resistance gene. Human-derived HuH7 hepatoblastoma cells were transfected with pMT-AAT/GFP using Lipofectamine Plus, and transfectants were selected in G418, 400 mg/mL. Comparison of fluorescence with phase contrast microscopy after 6 days suggested an approximate transfection efficiency of 20–30%. By 2 weeks after transfection, many surviving cells exhibited green fluorescence in discrete tubular structures typical of mitochondria when grown in standard selection medium; in some cells the fluorescence was strikingly intense. Particularly intense fluorescence was observed in some cells grown in selection medium supplemented with 100 mM ZnCl2. In such cells, cooled charged couple device (CCD) fluorescence microscopy detected non-mitochondrial fluorescent structures on or just beneath the PM. After 15 days of selection, cells were plated at low density, and 6 individual clones were selected and expanded in cloning cylinders. Two (#s 1 and 6) subsequently died out, but clones 2, 3, 4, and 5 continue to expand in the selection medium. By fluorescence microscopy, all exhibited green fluorescence, although none was as intense as the uncloned cells studied earlier. Using automated exposure times of high power fields in confluent culture dishes as an approximate measure of gene expression, the clones varied in their basal expression of mAspAT/GFP in the order 3>4>5>2. In all instances expression increased further when cells were cultured in zinc. On sodium dodecyl sulfate-polyacylamide-gel electrophoresis (SDS-PAGE)/immunoblotting, cell homogenates from clone 3 exhibited two protein bands, of ca. 44 and 75 kDa, reactive with monospecific polyclonal anti-mAspAT. The 75 kDa band also reacted with anti-GFP, and therefore represented the mAspAT/GFP fusion protein.

Conclusions: Following transfection of HuH7 cells with pMT-AAT/GFP, a 75 kDA mAspAT/GFP fusion protein is expressed in mitochondria, and, in small amounts, at the PM. Combined with real-time fluorescence microscopy, pMT-AAT/GFP may permit direct visualization of the pathway by which mAspAT reaches the PM.

Conventional Nucleic Acid-Based Hepatitis C Virus Genotyping Methods Exaggerate Differences Between Isolates. J.L. Walewski[1], D.D. Stump[1], T.R. Keller[2], and A.D. Branch[1]. [1]Liver Diseases, Department of Medicine, and [2]Abdominal Organ Transplantation, Department of Surgery, Mount Sinai School of Medicine, New York, NY.

Current systems for hepatitis C virus (HCV) genotype assignment are based on nucleic acid sequence analysis. They emphasize lines of descent and divergent evolution. This approach has the potential to exaggerate differences between isolates. Degeneracy in the genetic code makes it possible for two sequences to be only distantly related at the nucleic acid level and identical at the amino acid level. Since amino acid sequences may have a stronger correlation with pathogenicity than nucleic acid sequences, we are comparing the protein sequences of HCV isolates, beginning with the core.

Methods: 109 full-length Hepatitis C core nucleic acid sequences were retrieved from the GENBANK database. After pairwise alignment, by the MEGALIGN package (Lasergene, DNAstar, Madison, WI) using CLUSTAL algorithm (identity tables), phylogenetic dendrograms were generated. Percent similarities equal the homologies corrected for gaps.

Results: Percent similarities between isolates based on amino acid sequences were generally greater than those based on nucleic acid analysis. In some cases, 2 sequences of the same subtype (genotype 1 subtype b) were less similar than 2 sequences of different genotypes.

Conclusions: In the core region, family trees based on nucleic acid sequence analysis do not always correlate with those based on amino acid sequence analysis. Nucleic acid based trees exaggerate differences between isolates.

To correlate HCV sequences with disease manifestations, it may be necessary to divide HCV isolates into groups related by their functional properties rather than by their ancestry, which is reflected in their nucleic acid sequence.

Ceruloplasmin Levels in End-Stage Liver Disease. E.O. Atillasoy[1], S. Mehta[1], A.D. Min[1], S. Ozdemir[1], N. Copur[1], N. Bach[1], M. O'Rourke[1], K. Flynn[1], I. Volenberg[2], H. Bodenheimer[1], and M.L. Schilsky[3]. [1]Division of Liver Diseases, Mount Sinai School of Medicine, Mount Sinai School of Medicine, New York, NY; [2]National Center for Study of Wilson's Disease and [3]Albert Einstein College of Medicine, Bronx, NY.

Low ceruloplasmin (Cp) oxidase activity (< 20 mg/dL) and elevated non-Cp (free) Cu are present in most untreated Wilson's disease (WD) pts. We have shown that immunologically-derived serum Cp is normal in non-WD fulminant hepatitis {FHF} (Hepatology 1996; Suppl A:291).

Aim: To determine whether Cp or free Cu are altered in cirrhosis and non-WD FHF.

Methods: Study group: 66 unselected transplant candidates (M43, F23) Child's A ((M9, F5), Child's B (M25, F14), Child's C (M9, F4); chronic hepatitis (M3, F7); and FHF (M2, F4). Diagnoses of non-FHF pts were hepatitis C virus (HCV) (n = 29), HCV/ETOH (n = 12), ETOH (n = 6), cryptogenic (n = 7), primary biliary cirrhosis/primary sclerosing cholangitis (PBC/PSC) (n = 11), and miscellaneous (n = 11). Serum Cu was determined by spectroscopy, and Cp by oxidase activity and by Western blot (A.U.). Free Cu = total Cu - Cp Cu content.

Results: Cp levels (Mean ± SD) by oxidase (OXI) and immunologic (IMM) methods by group are in the table below:

Cp	Hepatitis	Child's A	Child's B	Child's C	FHF
OXI	4.4 ± 8.8	42.0 ± 13.8	36.8 ± 8.9	29.0 ± 7.2	29.7 ± 11.4
IMM	253 ± 416	372 ± 234	456 ± 349	359 ± 302	NA

Oxidase-derived Cp was different among the 5 groups ($p < 0.004$). Cp was lower in Child's C than Child's A and hepatitis pts ($p < 0.005$), and lower in FHF pts than hepatitis pts ($p < 0.05$). No significant differences were noted for Cp derived immunologically. Cp did not correlate with alanine amino transferase (ALT), albumin, prothrombin time (PT), cholesterol, or bilirubin. Cp < 20 mg/dL was seen in one WD FHF pt. Free Cu was > 25 μg/dL in nearly 30% (16/55) of non-FHF pts.

Conclusions: (1) Circulating levels of Cp are within the normal range but reduced with advanced liver disease. (2) Although free Cu may be elevated in some pts with non-WD liver disease, Cp oxidase method remains a valid screening tool for WD even in pts with hepatic insufficiency and FHF.

Thyroid Function in Liver Transplant Candidates. E.O. Atillasoy[1], N. Copur[1], A.D. Min[1], S. Ozdemir[1], M. O'Rourke[1], K. Flynn[1], C. Miller[1], C. Bodian[2], H. Bodenheimer[1], and R. Oren[3]. [1]Recanati/Miller Transplantation Institute and [2]Biomathematical Sciences, Mount Sinai School of Medicine, New York, NY; and [3]Marion Bessin Liver Research Center, Albert Einstein College of Medicine, New York, NY.

Thyroid status may affect the clinical course of various liver diseases. We have shown that hypothyroidism ameliorates portal pressure (Dig Dis Sci 1995; 40), prevents the development of cirrhosis (Hepatology, 1996; 24) and decreases the severity of fulminant hepatic failure (Hepatology 1998; 27) in rat models. We initiated a prospective pilot study to determine the relationship between thyroid and liver function in a cohort of unselected liver transplant candidates. Biochemical parameters and Child's class were recorded for each patient. Three patients on Synthroid were excluded.

Results: The diagnoses of 96 patients (M = 59, mean age 52 ± 10 yrs) were hepatitis C virus (HCV) (n = 36), ETOH (n = 15), HCV/ETOH (n = 16), cryptogenic (n = 12), primary biliary cirrhosis/primary sclerosing cholangitis (PBC/PSC) (n = 10), autoimmune (n = 2), and miscellaneous (n = 5). There were 34 Child's A, 46 Child's B, and 16 Child's C patients. Total bilirubin and synthetic function, as measured by albumin, total cholesterol and Prothrombin time, correlated with Child's class. Thyroid function for most patients was within the normal range and are depicted by Child's class in the Table. Thyroid-secreting hormone (TSH) was assayed using a third generation assay (Immulite, DPC, Los Angeles, CA).

Median	Child's A	Child's B	Child's C	p value*
TSH	1.7 (0.5 – 5.1)	2.3 (0.56.3)	2.3 (1.0 – 14.6)	0.03
T3	116 (59 – 102)	5.5 (50 – 218)	74 (39 – 104)	0.0001
Total T4	7.2 (4.2 – 12.1)	7.3 (4.0 – 11.4)	6.1 (4.1 – 9.5)	0.03

* by Kruskal-Wallis test

We did not find significant correlations between TSH and individual biochemical parameters. However, T3* and T4^ correlated with albumin (p = 0.0005*, p = 0.03^) and correlated inversely with PT (p = 0.01*, p = 0.01^) and total bilirubin (p = 0.008*, p = 0.01^).

Conclusions: (1) T3 and T4 levels decrease while serum TSH levels increase as Child's Class worsens. The mechanisms and implications of these changes deserve further investigation.

Neoplastic Diseases

Cellular Retinol Binding Protein Underexpression in Breast Cancer: An *in Situ* Hybridization Study. Y.S. Kuppumbatti[1], I. Bleiweiss[2], and R. Mira-y-Lopez[1]. [1]Department of Medicine, Division of Neoplastic Diseases, and [2]Department of Pathology, Mount Sinai School of Medicine, New York, NY.

Cellular retinol binding protein (CRBP) is a cytosolic protein that binds retinol (vitamin A) with high affinity. Unlike free retinol (ROL), ROL bound to CRBP (holo-CRBP) is channeled through specific metabolic pathways. ROL metabolism is an essential step in ROL signaling because ROL itself is not a ligand for the RAR and RXR families of ligand-dependent transcription factors. RARs and RXRs (in the form of RXR-RAR heterodimers or RXR-RXR homodimers) bind and are activated by ROL metabolites, chiefly retinoic acid and 4-oxo-ROL, and mediate all biological effects of ROL, safe for vision. Previous work in our laboratory showed that most (10 of 13) human breast cancer cell lines do not express detectable levels of CRBP mRNA, whereas normal human breast epithelial cells express abundant CRBP message. We wished to determine the extent of CRBP underexpression *in situ*; is it a common event, as suggested by our cell line screen, or is it a rare event? To do this, we used the technique of *in situ* hybridization (ISH) with digoxigenin-labeled hCRBP anti-sense and sense riboprobes. Hybridization products were visualized after reaction with an anti-digoxigenin antibody coupled to alkaline phosphatase. Formalin-fixed, paraffin-embedded sections of MDA-MB-468 and MCF-7 breast cancer cells (CRBP +ve and -ve by Northern analysis, respectively), as well as sections of normal human breast tissue, were used to test and optimize the method. Specific staining of MDA-MB-468 cells and normal breast ducts was obtained using a 320 bp hCRBP anti-sense riboprobe (corresponding to part of exon 2, exon 3, and part of exon 4), a 1/2000 antibody dilution, and a color development time of ~ 8 hrs. As expected, MCF-7 cells were not stained. We have now begun to apply the method to sections of human breast cancer specimens. Initial results (sections from 12 specimens analyzed) suggest that CRBP underexpression *in situ* occurs in 50% of cases and thus appears to be a frequent event.

Certain Pyrethroid Compounds Act as Xenoestrogens in MCF-7 Human Breast Carcinoma Cells. V. Go[1,3], J. Garey[2], M.S. Wolff[2], and B.G.T. Pogo[3]. [1]Molecular Basis of Diseases Program, [2]Department of Community and Preventive Medicine, and [3]Department of Medicine, Division of Neoplastic Diseases, Mount Sinai School of Medicine, New York, NY.

Estrogen regulates breast development and carcinogenesis. Equally important, numerous exogenous estrogens and xenoestrogens can disrupt this endocrine system. The worldwide use of synthetic pyrethroid compounds as insecticides as well as treatments for human head lice and scabies result in an increased potential for human exposure. Pyrethroid compounds have been shown to disrupt endocrine systems including thyroid hormone and androgen regulation in rodents and in humans. Since we were aware that some pyrethroids were capable of disrupting at least two endocrine systems, we examined the estrogenic potential of four synthetic pyrethroid compounds, sumithrin, fenvalerate, *d-trans*-allethrin, and permethrin, to determine if these compounds could disrupt estrogen regulation in breast carcinoma cells. We examined expression of pS2, an estrogen responsive gene, by northern analysis in MCF-7 cells.

Our results revealed that sumithrin and fenvalerate were potent inducers of pS2 expression at micromolar concentrations. However, only sumithrin-induced pS2 expression could be blocked by the antiestrogen ICI 164,384. In contrast, *d-trans*-allethrin alone was unable to affect pS2 mRNA levels, but in combination with estrogen, micromolar concentrations of *d-trans*-allethrin were sufficient to inhibit estrogen-induced pS2 expression. Permethrin alone, or in combination with either ICI 164,384 or estrogen, did not elicit any response. MCF-7 cell proliferation has also been assayed in the presence of these pyrethroid compounds.

In conclusion, we find that some pyrethroid compounds are able to disrupt estrogen homeostasis *in vitro*. Our results suggest that these pyrethroid compounds are "hormone disruptors" and that they may function through more than one signaling pathway.

Overexpression of Deletion-Mutant Epidermal Growth Factor Receptor Does Not Inhibit *p53* Induction in Human Glioblastoma Multiforme. U. Schmidt, M.-E. Halatsch, and T. Ohnuma. Division of Neoplastic Diseases, Mount Sinai School of Medicine, New York, NY.

In glioblastoma multiforme (GBM), the epidermal growth factor receptor (*EGFR*) gene is frequently rearranged, resulting in a specific in-frame deletion of 801 bp (nt 275 – 1075) of the coding sequence of the extracellular domain. The truncated receptor has been implicated in promoting survival of GBM cells by inhibiting apoptosis. Given the important role of *p53* and *MDM2* in the regulation of apoptosis, we examined the effect of UV irradiation on the induction of these genes in the presence of wild-type (wt) or deletion-mutant (delta) *EGFR*. We used the human glioblastoma cell line U-87MG which expresses endogenous wt*EGFR* and a related cell line which was generated by retroviral infection of the parental U-87MG cell line and overexpresses exogenous delta*EGFR* (U-87MG.delta*EGFR*). Twenty-four hrs following UV irradiation with doses of 0, 2, 8, 16 and 40 J/m^2, respectively, total cellular RNAs were isolated from these cell lines, treated with DNase I and subjected to reverse transcription using oligo(dT) primers. The resulting cDNAs were amplified by semi-quantitative polymerase chain reaction (PCR) employing sets of primers for the *EGFR*, *p53*, or *MDM2* target genes, respectively, and the β-actin reference gene. Parts of the PCR-reaction mixtures were separated on ethidium bromide-stained agarose gels which yielded sharp and distinct bands in accordance with the predicted sizes of the PCR products; photographs of the gels were assessed for differences in band intensities. In U-87MG, both wt*EGFR* and *p53* mRNA expressions were induced in a dose-dependent manner at 2, 8 and 16 J/m^2, compared to cells that received no UV irradiation; at 40 J/m^2, induction was present but reduced to levels below those observed at 2 J/m^2. In U-87MG.delta*EGFR*, no induction of delta*EGFR* mRNA was detected in the tested dose range, whereas *p53* induction was virtually identical to U-87MG. In accordance with our earlier observation that a TGC→TGA (CYS→STOP) nonsense mutation is present in codon 124 within the DNA binding domain of the *p53* gene (Proc Am Assoc Cancer Res 1998; 39:549), UV-dependent *p53* mRNA induction did not alter *MDM2* expression in any of the cell lines, consistent with failure of truncated *p53* to transactivate *MDM2*. These findings indicate that wt and delta*EGFR* expression are differentially regulated and that *p53* induction following DNA damage is independent of *EGFR* status. Our data suggest that the apoptotic resistance of U-87MG.delta*EGFR* cells is not attributable to a direct inhibitory effect exerted by delta*EGFR* on *p53*.

Bisulfite DNA Methylation Analysis of the Human Cellular Retinol Binding Protein Gene in Breast Cancer Cells. A. Arapshian, and R. Mira-y-Lopez. Division of Neoplastic Diseases, Mount Sinai School of Medicine, New York, NY.

Cellular retinol binding protein (CRBP) is a cytosolic protein that binds retinol with high affinity. Unlike free retinol (ROL), ROL bound to CRBP (holo-CRBP) is channeled through specific metabolic pathways. ROL metabolism is an essential step in ROL signaling because ROL itself is not a ligand for the RAR and RXR families of ligand-dependent transcription factors. RARs and RXRs (in the form of RXR-RAR heterodimers or RXR-RXR homodimers) bind and are activated by ROL metabolites, chiefly retinoic acid and 4-oxo-ROL, and mediate all biological effects of ROL, safe for vision. Previous work in our laboratory showed that most (10 of 13) human breast cancer cell lines do not express detectable levels of CRBP mRNA and protein, whereas normal human breast epithelial cells express abundant CRBP mRNA and protein. Southern blot analysis suggested that hypermethylation of the CRBP CpG island is a frequent mechanism of CRBP inactivation. To identify CpG dinucleotides that are specifically methylated in CRBP-non-expressing cells (such as MCF-7 cells), we are using the bisulfite method of DNA methylation analysis. Because the bisulfite reaction is highly single-strand-specific, test DNA must first be denatured by alkali treatment. It is then reacted with bisulfite, which results in the hydrolytic deamination of non-methylated cytosines, yielding uracil residues. Primers that are specific for binding to the modified DNA are then used to amplify the target sequence by polymer chain reaction (PCR). Unmethylated, modified Cs are amplified as Ts, whereas methylated Cs remain unmodified. We have used a plasmid encoding the hCRBP promoter and 5'-UTR region to optimize the bisulfite method. We have succeeded in obtaining a 96% rate of cytosine deamination. Among the parameters we found to be critical for successful deamination were the initial denaturation conditions, the commercial source of bisulfite, and primer design. We are currently applying the bisulfite method to genomic DNA from MCF-7 cells and MDA-MB-468 cells (CRBP-expressing).

Retrovirus-Mediated Transfer of a Hairpin Ribozyme Against Deletion-Mutant Epidermal Growth Factor Receptor mRNA Drastically Inhibits Anchorage-Independent Growth of Glioblastoma Target Cells *in vitro*. M.-E. Halatsch, U. Schmidt, I.C. Bötefür, J.F. Holland, and T. Ohnuma. Division of Neoplastic Diseases, Mount Sinai School of Medicine, New York, NY.

Glioblastoma multiforme (GBM) is among the most devastating of human malignancies. At least 75% of all patients die within 18 months of diagnosis. Amplification of the epidermal growth factor receptor (*EGFR*) gene is frequently present in primary GBM, occurs almost exclusively in this type of brain tumor and thus appears to be a late event in glial tumor progression. A significant fraction of the amplified genes are rearranged to specifically eliminate a DNA fragment containing exons 2 – 7 of the gene, resulting in an in-frame deletion of 801 bp (nt 275 – 1075) of the coding sequence of the extracellular domain. This deletion is considered the most prevalent mutation involving the *EGFR* gene with an incidence of up to 58% in GBM. The deletion-mutant (delta) *EGFR* is constitutively (ligand-independently) activated and has been shown to confer enhanced tumorigenicity *in vivo*. As a result of the deletion-mutation, the fusion-junction of the gene is created directly upstream of a ribozyme target codon (GUA). Based on efficiency and specificity testing in a cell-free system, we have previously identified a hairpin ribozyme derived from the negative strand of satellite RNA from chicory yellow mottle virus (sCYMV1) as a potential tool to specifically cleave delta*EGFR* mRNA. The anti-delta*EGFR*-sCYMV1 gene was subsequently cloned into the retroviral plasmid N2A+$tRNA_i^{met}$ directly downstream of a tRNA gene; expression of the chimeric tRNA-ribozyme transcript was controlled by an RNA polymerase III (pol III) promoter and a pol III transcription termination signal. High-titer recombinant retrovirus-containing supernatants ($> 1 \times 10^5$ cfu/mL as determined by infection of NIH/3T3 fibroblasts) derived from an amphotrophic GP+*env*AM 12 packaging cell line transfected with the N2A+$tRNA_i^{met}$-anti-delta*EGFR*-sCYMV1 construct were used to introduce the sCYMV1 hairpin ribozyme gene into U-87MG.delta*EGFR* glioblastoma cells which overexpress exogenous deltaEGFR. Using a virus:target cell ratio of 40:1 in the absence of drug selection, the ribozyme gene transfer resulted in > 90% reduction of delta*EGFR* mRNA levels, 69% inhibition of delta*EGFR*-mediated proliferation advantage and > 95% decrease of colony formation in soft agar under relative serum starvation conditions *in vitro*; transfer of a mutant control ribozyme which was rendered incapable of cleaving its target did not yield any of these effects. Our findings indicate that the anti-delta*EGFR*-sCYMV1 hairpin ribozyme is capable of specifically inhibiting the expression of delta*EGFR* and reversing the delta*EGFR*-associated malignant phenotype of GBM cells. This strategy may constitute a promising gene therapeutic approach for a molecularly defined subgroup of GBM.

Detection and Identification of Intact Complexes of Antineoplastic Drugs with Albumin and Hemoglobin Using Electrospray Mass Spectrometry. J. Roboz, L. Deng, and L. Ma. Division of Neoplastic Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Objectives: Use electrospray (ESI) mass spectrometry to measure the molecular masses of the complexes formed in the binding of suramin, etoposide, and actinomycin-D to albumin (Alb) and hemoglobin (Hb). Study: (a) Number of molecules bound under different molar ratios, incubation times and temperatures; (b) Binding of suramin to Alb in serum under toxic conditions.

Methods: Binding experiments: Molar ratios (Alb or Hb to drug): 5:1, 2:1, 1:1, 1:2, 1:5, 1:10, 1:25, 1:50, 1:100. Incubation: 0 – 1 hr in 6 steps, 1 – 48 hr in 6 steps; 37°C 10 µL. Aliquots were injected directly; carrier: 50% acetonitrile (AcCN) + 0.1% HCOOH at rate 5 µL/min flow. Suramin in serum: To 50 µl diluted (1:10 with buffer) normal human serum, serum (3.75 nmole Alb) suramin was added to provide molar ratios: 1:2; 1:4; 1:8. Incubation: 30 min, 37°C. ESI conditions: Mass range:1000 – 2000 amu/10 sec; cone voltage: 38 V. Molecular masses were determined using transformation software.

Results: Intact complexes of the 3 drugs with both Alb and Hb were detectable up to 95 kDa. The binding could not be reversed by subsequent addition of large protein excesses. Suramin: At ratios of 2:1, 1:1, and with excess Alb, only 1 and 2 suramins bounded. Suramin binding increased up to 20 molecules with increasing suramin excess (and incubation time); e.g., complexes containing up to 16 suramins were seen at 100:1 ratio. Suramin-Alb complex in serum: The ratio at therapeutic doses is ≈ 2:1. Only 2 suramins bound at 1:1, but up to 5 suramins were bound at 4:1 ratio. The toxic dose of 8:1 revealed complexes with up to 10 bound suramins, and free Alb could no longer be detected. Etoposide: The number of bound etoposides also increased with increasing drug:protein ratios and incubation times; e.g., up to 5 etoposides at various ratios when incubated for 1 hr. Maximum number of bound etoposides was 8 for both Hb (50:1 ratio, 3 hrs) and Alb (1:1, 48 hrs). Actinomycin-D: Behavior was similar to that of etoposide: maximum numbers detected: 3 with Alb (1:1, 48 hrs) and 8 with Hb (50:1, 48 hrs).

Conclusions: The binding of the surprisingly large number of drug molecules can only be explained by assuming changes in the secondary and/or tertiary structure of the proteins. Knowledge of the quantity, and half-lives of the complexes will lead to an understanding of the unusual displacing activity of suramin, and the possible monitoring of selected complexes in serum for toxicity. (Supported by the T.J. Martell Foundation for Leukemia, Cancer and AIDS Research).

Effects of Retrovirus-Mediated Transfer of Anti-*MDR*1 Ribozymes on the Restoration of Chemosensitivity of Multidrug Resistant Human Lymphoma Cells: Animal Study. F.-S. Wang, T. Ohnuma, and J.F. Holland. Division of Neoplastic Diseases, Mount Sinai School of Medicine, New York, NY.

Multidrug resistance (MDR) in human cancer seriously limits the efficacy of anticancer agents. Circumvention of MDR is one of the urgent goals in cancer chemotherapy. The molecular basis of MDR has been demonstrated to be multifactorial. Among these multiple factors, overexpression of *MDR*1 gene is a well-characterized mechanism of MDR. One strategy to block the overexpression of *MDR*1 is to use a ribozyme (Rz) targeted against *MDR*1 mRNA. We examined whether Rzs targeted against *MDR*1 mRNA were able to completely restore chemosensitivity of MDR tumor. MDR Daudi lymphoma cells were developed by infection of pHa*MDR*1/A retroviral vector (Gottesman). The infected cells were 20-fold resistant to vincristine (VCR) (Daudi/MDR_{20}). Four DNA sequences of anti-*MDR*1 Rzs; first, an original Rz directed against the GUC sequence at codon 196 (196*MDR*1-Rz); second, a stem-II modified Rz directed against the same GUC sequence (196*MDR*1-sRz); third, at the translation initiation site of MDR1 mRNA (i*MDR*1-sRz); and fourth, mutated i*MDR*1-sRz, were constructed into the retrovirus vector N2A+$tRNA_i^{met}$. These constructs were transfected into GP+*env*AM 12 packaging cells, and the supernatants containing the packaged retrovirus were used to infect Daudi/MDR_{20} cells. The Rz-transduced Daudi/MDR_{20} cells, Daudi/MDR_{20}-196*MDR*1-sRz and Daudi/MDR_{20}-i*MDR*1-sRz, completely restored chemosensitivity to vincristine and doxorubicin (MTT assay). Daudi/MDR_{20}-196*MDR*1-Rz cells were 2-fold more resistant as compared to wild type (wt) cells, and transduction of mutated Rz had no effects on the drug sensitivity. Male SCID mice were randomized to receive 1 x 10^7 cells IV of either Daudi/wt, Daudi/MDR_{20}, Daudi/MDR_{20}-196*MDR*1-Rz, Daudi/MDR_{20}-196*MDR*1-sRz, or Daudi/MDR_{20}-i*MDR*1-sRz. The mice were then treated with saline or VCR 0.45 µg/g body weight ip qd on days 2 – 6. Saline-treated mice inoculated with the lymphoma cells all died within 20 days. VCR-treated mice bearing Daudi/MDR_{20} also died within 17 days. In contrast, 120 day survival of VCR-treated mice bearing Daudi/wt, Daudi/MDR_{20}-196*MDR*1-Rz, Daudi/MDR_{20}-196*MDR*1-sRz, or Daudi/MDR_{20}-i*MDR*1-sRz cells was 50%, 33%, 33% and 50%, respectively. In a second study, mice were randomized to receive 3 x 10^6 wt or Rz transduced cells IV and were then treated with saline or VCR. Saline-treated mice inoculated with the lymphoma cells all died by day 25. VCR-treated mice bearing Daudi/MDR_{20} or Daudi/MDR_{20}-mut-i*MDR*1-sRz also died by the day 24. In contrast, with VCR treatment, 120 day survival of mice bearing Daudi/wt, Daudi/MDR_{20}-196*MDR*1-sRz, or Daudi/MDR_{20}-i*MDR*1-sRz was 80%, 83% and 100%, respectively. These data show that Rzs are capable of complete reversal of MDR. Our data have strong clinical implications.

Azacitidine (AzaC) Acts as a Biological Response Modifier on Hematopoietic Cell Response to Cytokines. L.R.. Silverman, S. Zinzar, and J.F. Holland. Department of Medicine, Division of Neoplastic Diseases, Mount Sinai School of Medicine, New York, NY.

Three Tumor-Associated Missense Mutations Indicate That Transcriptional Activation, Not Repression Is Critical for Growth Suppression by the WT1 Tumor Suppressor Protein. M.A. English, J.C. Reddy, and J.D. Licht. Department of Medicine and Brookdale Center for Developmental and Molecular Biology, Mount Sinai School of Medicine, New York, NY.

Nephrology

Hypernatremia with Edema in Seriously Ill Patients. T. Kahn. Nephrology Section, Bronx VA Medical Center, Bronx, NY; and Mount Sinai School of Medicine, New York, NY.

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Prevention of Intradialytic Hypotension with Patient-Temperature Dialysate (PTD): A Randomized Controlled Trial. M. Gabor, C. Gabor, K. Vitting, and J.R. Sterrett. Department of Medicine, Nephrology Division, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Hemodialysis is often complicated by episodes of hypotension during or after treatment. Previous studies have suggested that the common practice of using a dialysate at a set temperature of 37°C might induce vasodilation-related decrease in blood pressure. The goal of this study was to assess if using the patient's body temperature predialysis (PTD), as routinely measured by ear thermometer as the dialysate temperature, will reduce the frequency of intradialytic hypotension in the selected 28 patients. Each patient was randomly assigned to a pattern of 3 study treatments and 3 control treatments. Prior to each treatment the dialysate-temperature indicator on the dialysis machine was set either to match the patient's body temperature by ear thermometer pre-dialysis (study treatment) or to the customary setting of 37°C (control treatment). During each treatment, the blood pressure was recorded every 30 minutes during dialysis. We calculated the mean arterial pressure (MAP) (2 x diastolic + systolic/3) of the pre- and post-dialysis blood pressures for each of the 6 treatments. The data were normally distributed. For statistical analysis, we used analysis of variance (ANOVA), Newman-Keuls post-hoc testing, and paired T test. Comparing the mean of the 3 MAP pre-dialysis versus post-dialysis for each study and control treatments, there was a statistical significant difference ($p < 0.0001$), confirming the known drop in blood pressure during dialysis. There was no difference in the mean of MAP at initiation of dialysis in study versus control treatments. We compared the change in the mean of MAP in the study treatments ($ds = -9.6$) versus control treatments ($dc = -11.04$). The difference was not statistically significant. These data suggest that using a dialysate at patient's temperature did not significantly altered the change in the blood pressure during dialysis, when compared to the standard 37°C dialysate.

Functional Characterization of a Mouse Organic Anion Transporter in Mammalian Cells. K. Kuze[1], P. Graves[2], P. Wilson[1], and G. You[1]. Department of Medicine, Divisions of [1]Nephrology and [2]Endocrinology, Mount Sinai School of Medicine, New York, NY.

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Urea Inhibits NaK2Cl Cotransport in Mouse Inner Medullary Collecting Duct (IMCD-3) Cells. D.M. Kaji. Renal Section, Bronx VA Medical Center, Bronx, NY and Department of Medicine, Division of Nephrology, Mount Sinai School of Medicine, New York, NY.

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Expression of K-Cl Cotransporter (KCC1) in Human Tissues. D.M. Kaji[1], and H. Liapis[2]. [1]Bronx VA Medical Center, Bronx, NY, and Department of Medicine, Division of Nephrology Mount Sinai School of Medicine, New York, NY; and [2]Department of Pathology, Washington University School of Medicine, St. Louis, MO.

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Pulmonary

Clinical Efficacy of Sputum Gram Stain and Culture in the Diagnosis of Community-Acquired Pneumonia. V. Somaraju, R. Theerthakarai, and M.A. Khan. Department of Medicine, St. Joseph's Hospital and Medical Center., Paterson, NJ.

Objective: To assess the clinical efficacy of sputum Gram stain and culture in the diagnosis of community-acquired pneumonia (CAP).

Setting: An 800-bed, tertiary-care, urban teaching hospital.

Methods: A prospective study in which sputum samples were obtained from 74 patients (42 males, 32 females, age 22–99 years). Inclusion criterion was the diagnosis of CAP evidenced by both respiratory symptoms and roentgenographic impression of pulmonary infiltrate. Sputum analysis included Gram stain and culture.

Results: Sputum specimens from all 74 displayed mixed respiratory flora with Gram stain. Seventy (95%) had normal oropharyngeal flora on culture. Only 4 patients (5%) yielded specific pathogenic organisms on culture: 2 had *Klebsiella pneumoniae* and one each had *S. pneumoniae* and *H. influenzae*. No patient required a change in antibiotic therapy as cultured isolates were, in all cases, sensitive to the antibiotics started on the day of admission.

Conclusion: Routine Gram stain and culture of sputum specimens may not have clinical value in the diagnosis or treatment of CAP.

The Impact of Routine Admission Chest Radiographs on the Medical Management of Patients in a Short-Term Inpatient Substance Detoxification Unit. U.G. Iheme, R. Ayinla, and J.D. Granderson. Pulmonary Service, Department of Medicine, North General Hospital, New York, NY.

Objective: To study the impact of routine admission chest radiographs on the medical management of patients admitted into the substance detoxification unit of a community hospital in East Harlem, New York City.

Methods: We performed a retrospective study of 511 patients for whom a total of 672 chest radiographs were done on admission to the substance abuse/detoxification unit of North General Hospital, New York, NY during the period January 1997 – March 1997. These chest radiographs were evaluated for the presence of abnormalities as documented in the official radiologists' reports. The medical records of the patients with abnormal chest radiograph reports were evaluated by 2 staff pulmonologists to determine the presence of an infectious or malignant process based on clinical and radiographic findings.

Results: 672 admission chest radiographic studies (periapical [PA] and lateral views) were done for 511 patients. Abnormal findings were noted in 51 (8%) of these studies: 9 (18%) of these abnormal radiographs were considered to be typical for an active infectious process; 12 (23%) were considered to be atypical for an active infectious process; 4 (8%) were considered typical for a malignant process; 5 (10%) were atypical for a malignant process; and 21 (41%) were not suggestive of an infectious or malignant process. Of the 9 patients with chest radiograph results suggestive of an active infectious process, only 2 (2%) received additional or special treatment based on the radiograph results; these 2 patients also had symptoms of infection including fever. One of these 2 patients was HIV-positive and tuberculin skin test-positive, and was eventually lost to follow-up before completion of a pleural biopsy; the other had a known cancer of the lung and responded to treatment with antibiotics for bacterial pneumonia. The cost of chest radiograph studies for this subgroup of patients in the 3-month study period was $114,200.00, with a projected annual cost of $457,000.00.

Conclusion: Routine admission chest radiographs do not appear to have a significant impact on the medical management of patients in a short-term substance detoxification facility. A more cost-effective approach might be to limit such studies to the subset of patients with additional risk factors for tuberculosis such as HIV-seropositivity, recent tuberculin skin test conversion, and/or clinical features of active chest infection. A large-scale study may be useful.

Serial Deep Breaths Partially Reverse Induced Bronchoconstriction in Asthma. S. John, E.N. Schachter, and G. Skloot. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

It has been observed that after a period of prohibition of deep inspiration (DI) during Methacholine (Mch) challenge in asthmatics, subsequent DIs do not result in significant bronchodilatation, although a trend toward significance is seen (Skloot et al., J Clin Immunol 1995; 96:2393). We hypothesized that without this prohibition, serial DIs following Mch challenge would result in enhanced airway smooth muscle relaxation. Previously, Prieto et al. (Ann Allergy 1993; 70:487) found that using the

1st or 2nd forced expiratory volume in one second (FEV1) obtained after each Mch dose did not significantly modify the PC20 in symptomatic asthmatics. We extended this protocol to include the third FEV1 routinely performed. Fifteen allergic asthmatics (mean baseline % predicted FEV1 ± SEM of 83 ± 2.4) were studied. They performed 3 baseline maximal expiratory flow volume (MEFV) maneuvers and subsequently inhaled diluent followed by $^1/_2$ log incremental doses of Mch. Three minutes after each inhalation, 3 successive MEFV maneuvers were carried out. The provocative concentration of Mch that caused a 20% decrease in FEV1 from diluent baseline (PC20) was determined separately using the first, second and third MEFV curves (PC20-1, 2, 3).

The results are shown below (mean ± SEM):

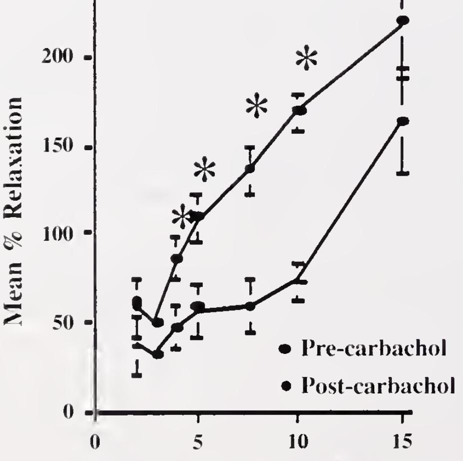
PC20-1	PC20-2	PC20-3
0.298 ± 0.075	0.368 ± 0.081*	0.414 ± 0.083†

*p = 0.04 for PC20-2 vs PC20-1; †p = 0.01 for PC20-3 vs PC20-1

PC20-2 and PC20-3 were significantly greater than PC20-1. Our data demonstrate that serial DIs do have a bronchodilatory effect on Mch-constricted asthmatic airways although multiple DIs may be needed before this effect is seen. We speculate that this ability to partially reverse induced bronchoconstriction with serial DIs in asthmatics may be a marker of mild disease and may decrease as disease worsens.

A Model for Studying the Role of Mediators in Airway Smooth Muscle Stretch-Induced Relaxation. S. John, G. Skloot, and E.N. Schachter. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Airway hyperresponsiveness in asthma may be a problem of limited smooth muscle relaxation with inspiration (Skloot et al., JCI 1995; 96:2393). One explanation for this reduced relaxation in asthmatics might be the impairment of a humoral mechanism. Pearse et al. (AJRCCM 1997; 4:A545) showed that stretch of airway tissue results in increased smooth muscle cyclic guanine monophosphate (cGMP). Based on this observation, we hypothesized that a humoral mechanism is involved in stretch-induced relaxation. We developed a model to test this hypothesis. Guinea pig tracheal rings were suspended in physiologic buffer and maintained at a baseline tension of 2 g. The rings were then stretched to different lengths by applying tensions from 2 – 15 g. After equilibration, tissues were washed and returned to 2 g tension. Carbachol (10^{-4} M) was added and the tissues allowed to reach maximal constriction. The response to stretch was again studied. The figure illustrates the relaxation response as a function of stretch, pre- and post-carbachol (*$p < 0.005$).



This model demonstrates relaxation of airway tissue following stretch and its enhancement in the presence of carbachol. We used the model to test several mediator modifying agents, including propranolol (a β-receptor antagonist), Nw-nitro-L-arginine methyl ester (L-NAME, a nitrous oxide synthase inhibitor), indomethacin (a cyclooxygenase inhibitor), and LY83583 (a cGMP reducing agent). A significant decrease in stretch-induced relaxation followed pre-treatment with LY83583, but only at the 10 g stretch level. No modification of stretch-induced relaxation occurred with pre-treatment by the other mediator modifying agents. These data suggest that cGMP may have a regulatory role in this process.

The Classification of Community-Acquired Pneumonia (CoCAP). R.E. Siegel. Patient Care Center Critical Care, Bronx VA Medical Center, Bronx, NY, and Department of Pulmonary/Critical Care Center, Mount Sinai School of Medicine, New York, NY.

A treatment algorithm was developed to facilitate switch from IV to oral antibiotics for inpatients with community-acquired pneumonia (CAP). The hospitalization decision is made on the basis of risk factors and patients are stratified as Low-Risk Pneumonia to be treated as outpatients, or High-Risk Pneumonia to be treated as inpatients. High-Risk Patients are categorized as Complicated Pneumonia or Unstable Pneumonia. Complicated Pneumonia includes patients with: systemic decompensation (impending respiratory failure, septic shock or multiorgan dysfunction syndrome); local extension or lung breakdown (lung abscess, necrotizing pneumonia or empyema); or metastic spread of infection (septic arthritis, meningitis or endocarditis). Unstable pneumonia includes patients with: chronic renal, heart or lung disease; uncontrolled diabetes, hyponatremia or volume depletion; immunocompromised host or high risk pathogen; change in mental status or inability to clear secretions; unstable vital sign, temperature > 101°F, acidosis or hypoxia; multi-lobar infection or pleural effusion; leukopenia or extreme leukocytosis; drug/alcohol withdrawal or suspected noncompliance; malnutrition or an inability to tolerate oral mediations; nursing hone resident or elderly fragile. Use of CoCAP along with criteria for clinical stability will encourage switch therapy and early discharge of the patient.

Efficacy of Early Switch Therapy for Inpatient Treatment of Community-Acquired Pneumonia. R.E. Siegel[1,3], M. Alicea[1], A. Lee[1], and R. Blaiklock[2]. [1]Patient Care Center Critical Care and [2]Pharmacy Department, Bronx VA Medical Center, Bronx, NY; and [3]Department of Pulmonary/Critical Care Center, Mount Sinai School of Medicine, New York, NY.

Between 1993 and 1997, 127 hospitalized veterans, mean age 59.9 years were treated for community-acquired pneumonia in 2 prospective, randomized research studies. Patients received IV cefuroxime (Zinacef™) 750 mg q8H and then oral cefuroxime axetil (Ceftin™) 500 mg q12H. There were 103 evaluable patients: 92/103 (89.3%) cures and 11/103 (10.7%) failures. There was no difference in cure rate in those treated with 2 days of IV cefuroxime prior to oral switch 89.4% (59/66) versus those treated with 5 – 10 days IV 89.2% (33/37). No difference was seen in cure rates with treatment duration (IV and oral) 7 day 87.5% (21/24) vs 10 day 89.9% (71/79). Etiologic diagnosis was made in 42/103 (40.8%). Of those with positive blood cultures and treated with 2 days of IV therapy 6/7 *S. pneumoniae* and 1/1 *S. aureus* were cured.

Our **conclusion** is that IV cefuroxime with a rapid step down to oral cefuroxime axetil is highly effective for inpatients with moderately severe community-acquired pneumonia. Prolonged IV antibiotic therapy does not improve the cure rate but increases the cost of care.

Sarcoidosis Presenting in the Older Population. R. Lenner[1], G.J. Schilero[1,2], M.L. Padilla[1], A.S. Teirstein[1]. [1]Department of Medicine, Division of Pulmonary and Critical Care Medicine, Mount Sinai School of Medicine, New York, NY; and [2]Pulmonary Section, Bronx VA Medical Center, Bronx, NY.

Purpose: Sarcoidosis is most common in patients between 20 and 40 years of age, but also occurs in children and older adults. Newly diagnosed sarcoidosis in older patients has not been characterized. The clinical, radiographic, and laboratory features of sarcoidosis presenting in patients 50 and older were compared to patients diagnosed at an earlier age.

Methods: The medical records of 181 patients over the age of 50 seen at The Mount Sinai Hospital with the diagnosis of sarcoidosis between January 1993 and January 1996 were reviewed. They were divided into 92 patients diagnosed at 50 years of age and older, and 89 whose diagnosis preceded age 50.

Results: The mean age at diagnosis of sarcoidosis was 58 and 39 years, respectively. Analysis revealed that the two groups were similar with regard to race, sex, smoking habits, PPD status, common presenting symptoms, laboratory values, organ system involvement, pulmonary function criteria, and radiographic stage. At the time of diagnosis, the commonest findings in both groups were respiratory symptoms (38% vs 37%) and abnormal chest roentgenograms (28% vs 34%). The two most prevalent pulmonary function test patterns were restrictive and (36% vs 27%) and normal (32% vs 31%). Most patients demonstrated either Stage I (32% vs 27%) or Stage II (37% vs 46%) chest roentgenograms. Organ systems most frequently involved included lung (96% vs 97%), lymph nodes (29% vs 35%), and skin (28% vs 33%). The two groups differed significantly with regard to two parameters: atypical chest pain as a presenting symptom was more common in patients diagnosed at a younger age (12% vs 1%), and Kveim tests were more likely to be positive in the younger population (69% vs 32%).

Conclusions: Sarcoidosis presents with similar clinical features whether diagnosed during young adulthood or over the age of 50. The Kveim test was less likely to be positive and atypical chest pain as a presenting symptom was less common in patients who were diagnosed with sarcoidosis at an older age.

Clinical Implications: Sarcoidosis is not uncommonly diagnosed in the older age group and presents in a manner similar to that seen in young adults. Since Kveim test positivity tends to wane with disease duration, the finding that the Kveim test was less likely to be positive in patients diagnosed after age 50 suggests that sarcoidosis may have been present for a long period of time prior to the diagnosis in these patients.

Cellular and Humoral Immune Dysfunction is Prevalent in Chronic Critically Ill Patients. N. Goldstein, D.M. Nierman, J.I. Mechanick, and T.H. Kalb. Division of Pulmonary/Critical Care, Mount Sinai School of Medicine, New York, NY

Infections frequently complicate RCU admissions and are associated with weaning failure. In this study, we sought to determine the incidence of cellular and humoral immune dysfunction in chronically critically ill patients with ventilatory failure, and to determine whether such defects were reversible. Upon transfer to the RCU, blood samples were drawn upon entry and repeated after 4 weeks. Cellular immune function was assessed by detecting lymphocyte proliferation after antigen incubation [candida/tetanus toxoid] *in vitro* (n = 11). Clinically healthy blood donors served as controls. Humoral immune response was assayed by specific antibody response to administered vaccine to T cell dependent [Hibtitre] and T independent [Pneumovax] antigens (n = 6). Demographic and clinical outcome data were collected by chart review.

On admission to the RCU, only one patient had a normal lymphocyte response to antigens (9%). Response to tetanus antigen was abnormally low in 6 patients and normal in 5 patients, whereas the response to candida was more likely to be supernormal (5 patients) than normal (2 patients) or low (four patients). Four patients had no initial response to either antigen. At 4 weeks after entry, 8 of 11 patients (73%) had weaned from ventilator assistance. Of antigen non-responders, 1 died of sepsis, 1 remained unresponsive and remained ventilator bound, and 2 patients reconstituted normal responses to both antigens and were weaned. Initial hyperresponsiveness to candida was associated with weaning success in 4 out of 5 patients. Weaning success at 4 weeks was associated with reconstitution of normal antigen response in 3 patients. Humoral response to Hibtitre was normal in all patients, though response to pneumococcal vaccine was subnormal in 60% of patients.

In conclusion, it appears that abnormal cellular and humoral immune responses are common in patients admitted to the RCU, and this may contribute to susceptibility to infection. Reconstitution of a normal response occurs in some patients, and this may correlate to weaning success. A remarkably exaggerated response to candida, perhaps due to exposure to candida at mucosal and intravenous sites, is commonly observed, though this does not correlate with weaning failure.

Results: *in vitro* lymphocyte response to specific antigen:

Response:	low	normal	supernormal
Tetanus	xxxxxx	xxxxx	
Candida	xxx	xx	xxxxxx
pneumovax			
Hibtitre			

Respiratory infection of the lower respiratory tract is a frequent finding in patients with long-term tracheostomies, usually associated with persistent upper tracheobronchial colonization. Pneumococcal vaccine is poorly immunogenic in "at risk" individuals, although the inability to respond is partially inherited.

Patients with long-term respiratory impairment and tracheostomy after acute critical illness have a number of metabolic and endocrine abnormalities including androgen and vitamin D deficiency. Vitamin D3 may play a role in immune integrity, in that it induces maturation and monokine production by macrophage like-cells, and aids in macrophage inhibition of *Mycobacterium tuberculosis* proliferation.

Airway Epithelial Cells Express Functional T Cell Co-Stimulator Molecules B7.1 and B7.2. I. Oei, K. Becker, I. George, K. Sperber, and T.H. Kalb. Divisions of Pulmonary/Critical Care and Clinical Immunology, Mount Sinai School of Medicine, New York, NY.

In conventional antigen presentation, the lymphocyte molecules CD28 and CTLA-4 play important costimulatory roles in the response to TCR engagement by Antigen-MHC class II molecule complex. Two ligands, B7.1 and B7.2, share binding avidity for both CD28 and CTLA-4, and are expressed on dendritic cells and other conventional stimulator cells. Human airway epithelial cells resemble conventional antigen presenting cells in that they can take up soluble antigen, express surface class II MHC molecules, and stimulate allogeneic and antigen-specific CD4+T lymphocyte activation and proliferation, though it is unclear whether AEC express functional B7.1 or B7.2. In one report, alveolar epithelium was devoid of B7.1. In the present study, we asked whether nasal or bronchial epithelium express B7.1 and B7.2, whether this expression is affected by exposure to interferon-gamma (IFN-gamma), and whether B7.1 or B7.2 are required for costimulation by AEC of antigen-specific T lymphocytes. By flow cytometry, we detected expression of B7.1 and B7.2 in freshly harvested human nasal and bronchial epithelial cells, and the expression of B7.2 was enhanced by IFN-gamma (400 u/mL, 48 hr). B7.2 message was detected by PCR in mRNA extracted from AEC and AEC cell line A549. B7.1 mAb BB1 partially inhibited the autologous T cell proliferation induced by coculture with antigen (candida/tetanus toxoid) pulsed nasal epithelial cells, whereas both B7.1 and B7.2 mAb inhibited stimulation induced by bronchial epithelial cells. These data support the notion that AEC may provide costimulation via regulated expression of B7.1 and B7.2.

Airway Resistance Is Increased in Subjects with Cervical Spinal Cord Injury. G. Schilero, D.R. Grimm, P.L. Almenoff, A.M. Spungen, W.A. Bauman, and M. Lesser. Department of Medicine, Bronx VA Medical Center, Bronx, NY.

Observations that approximately 45% of subjects with chronic cervical spinal cord injury (SCI) experience significant bronchodilation following inhalation of metaproterenol sulfate or ipratropium bromide, and that hyperresponsiveness to aerosolized methacholine correlates with lower baseline forced expiratory volume in one second (FEV1), suggesting that resting airway caliber is decreased in these subjects. Increased bronchomotor tone may account for airway hyperresponsiveness because resistance of the airways to gas flow is inversely related to the fourth power of the radius. A small further reduction in the radius of the airways with histamine or methacholine, therefore, would result in a much larger increase in resistance. Physiologic studies were conducted to determine whether resting airway resistance is increased in subjects with cervical SCI. Airway resistance (Raw) and thoracic gas volume (Vtg) were obtained using a variable-pressure, constant-volume body plethysmograph (Vmax Body Plethysmography, SensorMedics, Inc., Yorba Linda, CA). Airway resistance was measured during a panting exercise at two cycles per second and was converted to conductance (Gaw) by taking its reciprocal. Conductance and resistance were corrected for thoracic gas volume and expressed as specific conductance (sGaw) and specific resistance (sRaw). Data are presented as mean ± SD, $* = p < 0.05$ for quadriplegia vs paraplegia and controls.

Parameters	Control	Paraplegia	Quadriplegia
n	14	14	12
Vtg (liters)	4.15 ± 0.74	4.35 ± 1.08	3.45 ± 0.92
sRaw ($cmH_2O/L/s$)	3.72 ± 0.75	4.05 ± 0.66	7.27 ± 2.89*
sRaw (% predicted)	91 ± 15	93 ± 14	167 ± 63*
sGaw $(cmH_2O \cdot s)^{-1}$	0.27 ± 0.05	0.25 ± 0.04	0.15 ± 0.06*
sGaw (% predicted)	113 ± 19	110 ± 18	68 ± 25*

Our data demonstrate that airway resistance is increased in subjects with cervical SCI, indicating that baseline airway tone is elevated. The findings may explain why such subjects exhibit bronchial irritability to inhaled pharmacological agents. Potential causes for reduced airway caliber include acquired structural changes within airway walls, amplified parasympathetic (bronchoconstrictive) activity due to loss of sympathetic innervation of the lungs, or inability to maximally stretch airways because of reduced inspiratory capacity.

Comparison of Slow Vital Capacity (SVC) with Forced Vital Capacity (FVC) in the Diagnosis and Severity-Assessment of Airflow Obstruction. S. Manawar, A. Wojno-Oranski, and M.A. Khan. St. Joseph's Hospital and Medical Center, Paterson, NJ; and Seton Hall University, School of Graduate Medical Education, South Orange, NJ.

Relationship Between $PaCO_2$ Level and FEV_1 in Patients with Chronic Airflow Obstruction. A. Wojno-Oranski, S. Manawar, M. A. Khan. St. Joseph's Hospital and Medical Center, Paterson, NJ; and Seton Hall University, School of Graduate Medical Education, South Orange, NJ.

Role of the A8 Integrin Suhunit in Bleomycin-Induced Pulmonary Fibrosis. D.M. Levine[1], Y. Wang[1], T.A. Milner[2], and L.M. Schnapp[1]. [1] Department of Medicine, Division of Pulmonary and Critical Care Medicine, Mount Sinai School of Medicine, New York, NY, and [2]Cornell University Medical College, New York, NY.

Role of CT Scan of the Chest in the Radiographic Staging of Sarcoidosis. M. Ismail, A. Wojno-Oranski, and M.A. Khan. St. Joseph's Hospital and Medical Center, Paterson, NJ; and Seton Hall University, School of Graduate Medical Education, South Orange, NJ.

Detecting Obstruction in Restrictive Lung Disease. M. Ismail, S. Manawar, and M.A. Khan. St. Joseph's Hospital and Medical Center, Paterson, NJ; and Seton Hall University, School of Graduate Medical Education, South Orange, NJ.

Rheumatology

*** Long-Term Efficacy of Interferon-alpha (IFNa) for Extrahepatic Disease Associated with Hepatitis C Virus (HCV) Infection.** M. Naarendorp, U. Kallemuchikkal, and P.D. Gorevic. Department of Medicine, Division of Rheumatology, Mount Sinai School of Medicine, New York, NY.

Antiviral activity of interferon-α (IFNa) has been recently reported to correlate with clinical and biochemical improvement in several large series of patients with the syndrome of Mixed Cryoglobulinemia (MC) associated with chronic hepatitis C virus (HCV) infection from endemic areas in Italy and France. Only limited information is available, however, regarding the responsiveness of MC patients to this therapeutic agent in nonendemic areas and with regard to long-term follow-up. Eleven patients presenting with extrahepatic manifestations of HCV infection, including 10 with Type II (IgMk-IgG) cryoglobulins, were treated with IFNa. Of these, 45.5% were women and the average age was 48 years. Eight had cutaneous vasculitis, 7 neuropathy, and 4 membranoproliferative glomerulonephritis. Four of 6 bone marrows had increased numbers of lymphoid aggregates and/or clonal populations of lymphocytes by flow cytometry. Serologic testing revealed that all had antiglobulin activity restricted to the IgM isotype, 7 had elevated levels of total IgM that generally reflected disease activity, and 6 had significant depression of C4. All sera and cryoglobulins were seropositive by Western blot analysis using recombinant HCV antigens; all contained viral RNA by reverse transcription polymerase chain reaction (RT-PCR). In 7/ 9 patients studied, HCV RNA was repeatedly present in washed peripheral blood mononuclear cells (PBMC). Liver biopsies were performed on all patients prior to initiation of therapy, though only 5/11 had modest elevations of transaminases; all showed chronic hepatitis, with prominent lymphoid infiltrates in 5, and varying degrees of fibrosis in 6; 9/10 biopsies studied by RT *in situ* PCR were found to have viral RNA in hepatocytes. One patient was genotype Ia, 3 Ib, 2 IIb, 3 III, and 1 IV. Cryoglobulin levels prior to therapy ranged from 0.08–6.7 mg/mL, and HCV RNA, quantitated by Amplicor competitive PCR assay, 24,359 to 1,204,874 copies/mL. Duration of disease, based on clinical manifestations associated with MC, varied from 5 months–15 years, with 6 patients having received prior therapy with other agents, including corticosteroids in 5. All patients received 3M units IFNa tiw, with total length of treatment ranging from 3 months – 5 years. Three patients were withdrawn because of toxicity or progression of disease. Three patients were nonresponders at 6, 16 and a total of 17 months of therapy; one developed renal involvement while on treatment and one developed clinical and biochemical hyperviscosity syndrome. Three patients (27.2%) were complete responders, based on resolution of symptoms and disappearance of cryoprecipitates and HCV RNA, but only one was successfully weaned off IFNa after 3 years. IFNa is biologically active for treatment of extrahepatic HCV infection and may be safely tolerated for prolonged periods of time. Sustained clearance of virus was seen in only 1/11 cases, and careful monitoring is necessary to assess for virus in cryoprecipitates and PBMN, evolution of subclinical liver pathology, and progression of renal or neurologic disease.

Secretase Cleavage of the Amyloid Precursor Protein: The Role of Neural Processing Enzyme EP24.15. J.A. Ripellino[1], P.J. Crack[2], M. Blum[2], P.D. Gorevic[1], and M.J. Glucksman[2]. [1]Department of Medicine, Division of Rheumatology and [2]Fishberg Research Center in Neurobiology, Mount Sinai School of Medicine, New York, NY.

A hallmark of Alzheimer's disease is the extracellular deposition of amyloid in neuritic plaques and cerebral blood vessel walls. The primary constituent of these deposits is the 40–42 amino acid β-peptide (Abeta). Abeta is derived by proteolytic processing of a 110–135 kDa integral membrane protein, the amyloid precursor protein (APP), by enzymes referred to as 'secretases'. Although these enzymes have not been clearly identified, β- and gamma-secretases cleave APP at the N- and C- terminus of Abeta, respectively, to yield the amyloidogenic Abeta peptide. Several studies have implicated the metalloendopeptidase EC 3.4.24.15 (EP24.15) as a potential β-secretase candidate. This processing enzyme is a soluble metalloenzyme present intracellularly and extracellularly where it functions in modulating neuropeptide levels. M17 neuroblastoma cells, previously transfected with APPwt or APP containing the Swedish double mutation and then subsequently transfected with EP24.15, show a 4–5-fold increase in intracellular levels of EP24.15 activity and demonstrated an enhanced processing of full-length APP. The extracellular levels of secreted APP increased with a concomitant increase in intracellular Abeta levels. This activity could be further regulated by the addition of heparin to the conditioned medium. Our data indicate that EP24.15 may have a role in Abeta production.

Are IgA Antiphospholipid Antibodies a Technical Artifact? H. Eguchi, L.B. Keil, and V.A. DeBari. Department of Medicine, Division of Rheumatology, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Although the antiphospholipid syndrome (APS) derives its name from the association of autoantibodies (ab) to cardiolipin and other phospholipids (PL), more recent studies suggest that the true autoepitopes reside on PL-binding proteins such as $\beta_2$glycoprotein I (β_2GPI) and prothrombin. Among these ab, those of the IgA immunoglobulin class are the least well studied. In fact, it was recently proposed that they may be purely artifactual, the result of nonspecific binding (NSB) in the enzyme-linked immunosorbent assay (ELISA) systems used to detect them. Although we have, in the past, observed NSB of IgA to bovine serum albumin (BSA), more recently we have used an ELISA which does not include BSA. In this study, we examine the issue of NSB by IgA using a differential (Δ)

ELISA in which the values in the absence of antigen (-β_2GPI) are subtracted from those in its presence (+β_2GPI). ELISA absorbance (abs) from a group of 44 APS were compared those from a group of 51 healthy controls (con). Abs for APS + β_2GPI was 0.38 ± 0.73 (range 0.07–4.87). APS - β_2GPI yielded 0.13 ± 0.05 (range 0.09–0.44). Con + β_2GPI ranged from 0.06–0.88 (0.13 ± 0.14) and con - β_2GPI ranged from 0.12–0.22 (0.15 ± 0.02). When Δ abs were calculated for each case, APS were 0.24 ±0.69 compared to -0.02 ± 0.14 for con ($p < 0.0001$). Calibrators were applied and results were expressed in standard IgA anti-β_2GPI units (SAU). Con had 14 SAU as upper 95th percentile; 20 APS (45%) were above this cutoff. These data suggest that increased IgA NSB is not responsible for elevated β_2GPI binding by IgA from APS.

Enzyme Immunoassay of Major Immunoglobulin Class (IgG, IgA and IgM) Antibodies to β_GGlycoprotein I in Patients with Antiphospholipid Syndrome. S. Sawaged, V.A. Debari, and L.B. Keil. Division of Rheumatology, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Fluorescence Anisotropy Studies of β2Glycoprotein I. J.D. Kohles, V.A. Debari, and M. Petersheim. Seton Hall University, South Orange, NJ; and St. Joseph's Hospital and Medical Center, Paterson, NJ.

Inhibition of β_2Glycoprotein I Binding to Anionic Phospholipids. J.D. Kohles, M. Petersheim, and V.A. Debari. St. Joseph's Hospital and Medical Center, Paterson, NJ; and Seton Hall University, South Orange, NJ.

Spinal Cord Research

Leg Ergometry Training with Functional Electrical Stimulation Improves Body Composition and HDL-Cholesterol Values in Individuals with Spinal Cord Injury. W.A. Bauman, and A.M. Spungen. Department of Medicine, Bronx VA Medical Center, Bronx, NY.

Introduction: The positive benefits of exercise training on body composition and serum lipids in the general population have been well documented. Exercise training for persons with spinal cord injury (SCI) is limited to arm work or functional electrical stimulation (FES) of the legs. FES provides active exercise for the lower body in individuals with paralysis.

Objective: We addressed the effects of FES leg exercise training on body composition and serum high density lipoprotein-cholesterol (HDL-c) in subjects with SCI.

Methods: Twelve male subjects, 11 with quadriplegia and 1 with paraplegia participated in a 12-week (3 sessions/week) exercise training program. Each exercise session consisted of 3–6 runs of FES to fatigue and ranged from 2–30 minutes. Measurements for body cell mass, body composition and lipids were performed before and after the 12-week program. Body cell mass was measured by a total body potassium (TBK) 4-Pi counting chamber. Body composition was measured by dual energy x-ray absorptiometry (DEXA); measures of lean and fat tissue mass were compartmentalized by DEXA software for arms, trunk and legs. Thigh circumference was measured at the midpoint of the thigh length. TBK and DEXA studies were performed at St. Lukes/Roosevelt Hospital Center, New York, NY. Serum HDL-c was drawn in a fasted state and measured by SMAK (Technicon Instruments, Tarrytown, NY). The results are reported as mean ± SE.

Results: After 12 weeks of FES training, leg lean tissue mass significantly increased (15.3 ± 0.6 vs 17.2 ± 0.7 kg, $p < 0.0001$), leg percent fat significantly decreased (31.8 ± 2.3 vs 28.5 ± 2.4, $p < 0.005$), leg fat mass remained unchanged, and thigh circumference significantly increased (448 ± 15 vs 476 ± 14 mm, $p < 0.005$). Improvements in lean tissue mass of the legs were associated with a significant increase in total body lean tissue mass (46.5 ± 1.7 vs 49.2 ± 1.6 kg, $p < 0.001$). TBK significantly improved (2597 ± 108 vs 2768 ± 128 mEq, $p < 0.005$). Serum HDL-c significantly improved (37 ± 2 vs 41 ± 2 mg/dL, $p < 0.01$).

Conclusions: FES leg ergometry training produced positive changes in body composition and serum HDL-c in subjects with SCI, as has been demonstrated by non-FES exercise training in the general population. The positive improvements demonstrated herein may improve general health and reduce the risk factors for heart disease in individuals with SCI.

Transcutaneous Oxygen Levels in Individuals with Paraplegia and Pressure Ulcers. V. Teodorescu[1], M.H. Liu[2], and W.A. Bauman[3]. Departments of [1]Surgery, [2]Medicine, and [3]Spinal Cord Damage Resource Center, Bronx VA Medical Center, Bronx, NY.

Introduction: Individuals with spinal cord injury (SCI) have increased risk of developing pressure ulcers. Ulcer formation may be due to a variety of factors, including autonomic dysfunction which may result in abnormal regulation of peripheral blood flow. Mawson et al. (Arch Phys Med Rehabil 1988; 67:123–127) demonstrated significantly lower sacral transcutaneous oxygen tension (TcpO2) levels in healthy subjects with SCI than in able-bodied controls, suggesting decreased circulation at the measurement site.

Objective: This study investigated TcpO2 in subjects with paraplegia and pressure ulcer (PU-PARA) compared with both those with paraplegia and no pressure ulcer (NPU-PARA) and able-bodied subjects (control).

Methods: Twenty-one males participated in this study with 7 subjects grouped in each of the following categories: PU-PARA, NPU-PARA, and control. Except for pressure ulcers, all subjects were otherwise stable and not prescribed medications known to interfere with circulation. Peripheral blood flow was assessed by measurement of TcpO2 with the subjects resting in the supine position. The membrane electrode was calibrated at each designated site for 15 minutes. Following calibration, TcpO2 levels were recorded at 1 minute intervals for 5 minutes, and then averaged. In the NPU-PARA and control groups, the membrane electrode was placed at the right and left trochanter and then averaged. Measurement of TcpO2 for the PU-PARA was performed by placing the membrane electrode 1 cm from the pressure ulcer located on either trochanter, ischium, or sacrum. All pressure ulcers were either stage III or IV. A one-way analysis of variance (ANOVA) with post-hoc analysis was applied using Scheffe's pairwise comparisons; the level of significance was $p < 0.05$. Results are reported as mean ± SEM.

Results: Duration of injury was not significantly different between NPU-PARA and PU-PARA groups. The control group was significantly younger than both the PU-PARA and NPU-PARA groups (31 ± 3.20 vs 56 ± 6.00 and 52 ± 5.78 yrs, respectively, $p < 0.05$). No differences were found among the groups for height or weight. The TcpO2 was significantly lower in the PU-PARA group than in both the NPU-PARA and control groups (23.53 ± 1.83 vs 58.93 ± 2.53 and 79.70 ± 6.77 mm Hg, respectively, $p < 0.05$). Additionally, as we previously reported, the NPU-PARA group also demonstrated significantly lower TcpO2 than the control group.

Conclusion: Our results showed significantly lower blood flow in healthy persons with paraplegia compared with ambulatory individuals. Patients with pressure ulcers were demonstrated to have a further reduction in TcpO2 levels compared with the persons with paraplegia without pressure ulcers. The abnormal regulation of blood flow observed in the NPU-PARA group may be a factor in the increased risk of developing a pressure ulcer in SCI. Thus, the further attenuation of TcpO2 seen in PU-PARA group may be useful as a predictor of whether ulcers can heal with local care or whether more treatment is required.

Comparison of Ward Plating with Routine Processing of Urine Cultures. S.T. Brown[1], M. Rasul[2], A.M. Spungen[1], A. Shahidi[2], A.S. Cytryn[1], and W.A. Bauman[1]. [1]Department of Medicine and [2]Spinal Cord Damage Resource Center, Bronx VA Medical Center, Bronx, NY.

Introduction: Urinary tract infection (UTI) is the most common infectious complication in persons with spinal cord injury (SCI). Microbiolologic diagnosis of UTI, which depends upon quantitative cultures of urine, unreliably differentiates clinically relevant pathogens from contaminating organisms.

Objective: Preliminary results are reported comparing the effect of immediate ward plating with routine clinical processing on species and quantification of urine isolates.

Methods: The inpatient SCI Service of the Bronx VA Medical Center is composed of 2 physically separate wards: Ward 1D and Ward 1E. Data associated with urine cultures that were obtained for routine clinical indications was gathered from both wards. Fever was the most common reason for obtaining a urine culture (65%). Urine specimens from Ward 1D were processed by routine methods (Control). On Ward 1E, the urine specimen was split when collected. One sample (Routine Plating) was sent to the microbiology lab for routine processing and the other (Ward Plating) was plated on culture media within 15 minutes of obtaining the specimen. The first and second most common organisms identified by Ward Plating, Routine Plating and Control were analyzed.

Results: Nearly identical isolates were obtained on Ward and Routine Plating from 11 of 17 cultures. The remaining 6 cultures differed significantly with respect to the predominant organisms identified ($p = 0.018$, Fisher's Exact test). Four organisms were identified with counts = 100,000 by Routine Plating that were identified as < 100,000 by Ward Plating. Surprisingly, significantly fewer cultures were negative (0 counts) by Ward Plating than Routine Plating. Two specimens from Ward Plating grew organisms with = 100,000 counts that were not found by Routine Plating. Fewer organisms with counts = 100,000 were cultured from Ward and Routine Plating than from Control Plating. The most common first and second organisms identified for both Ward Plating and Routine Plating from Ward 1E and for Control from Ward 1D were *Streptococcus faecalis* (18%) and *Escherichia coli* (18%).

Conclusions: In these preliminary results, Ward Plating revealed significant differences in the identification of the predominate organisms obtained during the evaluation of UTI. Culture-guided treatment decisions could have led to altered antibiotic selection and clinical outcome. The differences between Wards 1E and 1D in rates of positive and negative cultures by routine processing most likely reflects improved collection techniques on Ward 1E due to a study effect. We concluded that Ward Plating may be a preferred method for processing specimens during evaluation of UTI.

Two Months of Therapy with an Anabolic Agent is Associated with a Significant Increase in Diaphragmatic Width. O.L. Dumitrescu[1], A.M. Spungen[2], M. Strakhan[3], and W.A. Bauman[2]. Departments of [1]Radiology and [2]Medicine, and [3]Spinal Cord Damage Resource Center, Bronx VA Medical Center, Bronx, NY.

Introduction: The diaphragm is innervated from cervical vertebrae 3 – 5. Individuals with complete lesions above C3 require mechanical ventilation. The completeness of the cord injury from C3 – C5 results in varying degrees of diaphragmatic paralysis. In persons with cervical lesions, the inspiratory and expiratory muscles of breathing are compromised to varying degrees. The diaphragm remains the most vital muscle for breathing in an individual with tetraplegia. Anabolic steroids have been used to increase muscle mass in general.

Objective: In an effort to improve diaphragmatic muscle mass, the anabolic agent oxandrolone was administered. Unlike other steroid anabolic agents, oxandrolone is well tolerated and has low potential for androgenic effects.

Methods: Seven subjects with tetraplegia (C4 – C7) were prescribed oxandrolone (20 mg/day) for 2 months. Diaphragmatic width was determined at baseline and after 2 months of treatment. A 5.0 MHz ultrasound transducer was used to image the diaphragm with the subject seated in a wheelchair. The 3 layers of the diaphragm were imaged with the transducer held perpendicular to the chest wall in the eighth or ninth right intercostal spaces, between the anteroaxillary and mid-axially lines, to permit measurement of the diaphragm at the zone of apposition. In each subject, 5–9 images were recorded for each measurement at baseline and month two. A blinded reader determined the width to the nearest 0.1 mm as the distance from the superficial edge of the diaphragmatic pleura to the deep edge of the peritoneum (McCool et al. Am J Respir Crit Care Med 1997; 155:1570-1574). A paired T test was used to determine differences in diaphragmatic width between baseline and month two. The results are reported as mean ± SD and percent change from baseline.

Results: The age of the study group was 38.9 ± 9.7 years (range of 26–51). All subjects were chronically injured, 15.6 ± 8.6 years (range 7–29). The subjects were non obese (body mass index [BMI] 22.42 ± 3.43 kg/m^2). The group consisted 1 current, 3 former (quit > 1 year), and 3 never smokers. Three subjects had complete and 4 subjects had incomplete lesions. Diaphragmatic width measurements at month two were significantly greater than at baseline (2.73 ± 0.23 vs 2.43 ± 0.29, paired $t_{(6)} = 3.334$, $p = 0.015$). There was an average improvement in the diaphragmatic width of 13.3 ± 11.6 percent (range of 0–30) from baseline measurements.

Conclusions: These preliminary findings suggest potential improvements in diaphragm mass associated with oxandrolone treatment. Whether these structural changes are correlated with increased diaphragmatic strength and functional improvement in breathing is being addressed in an ongoing study at present in our unit.

Impaired Prostacyclin Receptors in Platelets from Spinal Cord Injured Subjects: A Twin Study. N.N. Kahn, A.K. Sinha,. and W.A. Bauman. Department of Medicine, Bronx VA Medical Center, Bronx, NY.

Introduction: Premature coronary artery disease (CAD) is the leading cause of death in individuals with spinal cord injury (SCI).

Objective: To compare platelet function and prostacyclin binding in monozygotic twins, one twin in each pair having an SCI.

Methods: Platelets were studied for aggregation, inhibition of aggregation, prostanoid stimulation of cyclic adenosine monophosphate (AMP) synthesis, platelet-stimulated thrombin generation, and Scatchard analysis of prostaglandin E_1 binding. Platelets were collected from 12 pairs of monozygotic twins (confirmed by DNA analyses).

Results: Platelet aggregation with adenosine diphosphate (ADP), thrombin or collagen was similar in the SCI and nonSCI twin groups. Inhibition of platelet aggregation by prostacyclin (PGI_2) and prostanoid-induced cyclic AMP synthesis was comparable in the 2 groups. However, PGI_2 completely inhibited the platelet-stimulated thrombin generation in normals but failed to do so in those with SCI. Comparing SCI with nonSCI twins, Scatchard analysis of the binding of ^{3}H-prostaglandin E_1 showed a significant loss of high-affinity receptor number ($n_1 = 40 \pm 12$ vs $n_1 = 170 \pm 28$ sites/platelet, $p > 0.001$) with no significant change in receptor affinity ($kd_1 = 5.9 \pm 2.35$ vs $kd_1 = 7.9 \pm 2.9$ nM); platelet low-affinity receptor number ($n_2 = 1770 \pm 230$ vs $n_2 = 1798 \pm 443$ sites/cell) and receptor affinity $kd_2 = 1.02 \pm 0.3$ vs $kd_2 = 1.1 \pm 0.33$ μM) were not significantly different.

Conclusions: The occurrence of these platelet abnormalities in identical twins with SCI suggests non-genetic causes for CAD. These results indicate that the loss of inhibitory effect of PGI_2 on thrombin generation in the SCI twin was due to the loss of platelet high-affinity prostanoid receptors, which may contribute to atherogenesis.

Bronchial Hyperresponsiveness in Cervical Spinal Cord Injury is Associated with Reduced Baseline Pulmonary Function. M. Lesser, D.R. Grimm, P.L. Almenoff, A.M. Spungen, G. Schilero, and W.A. Bauman. Department of Medicine, Bronx VA Medical Center, Bronx, NY.

The mechanism of exaggerated bronchoconstriction observed in subjects with chronic cervical spinal cord injury following inhalation of pharmacological and physicochemical agents remains unexplained. To further explore pathogenesis of this phenomenon, spirometric and lung volume parameters from 34 consecutive subjects challenged with aerosolized histamine were evaluated. The study population included 27 responders (geometric mean dose at which there is a 2% reduction of FEV [PC20] = 1.32 mg/mL) and 7 non-responders (geometric mean PC20 = 21.19 mg/mL). Age, duration of injury, level of injury and completeness of injury did not differ significantly. Eight of 27 responders and 6 of the 7 non-responders were never smokers. Selected spirometric and lung volume parameters are listed; data are mean ± SD:

Parameters	Responders (n = 27)	Non-responders (n = 7)	
FVC (% predicted)	58 ± 15.01	60 ± 10.45	
FEV1 (% predicted)	60 ± 15.04	67 ± 10.38	
FEV1/FVC (%)	79 ± 11.23	85 ± 10.32	
FEF25-75 (% predicted)	58 ± 21.01	78 ± 20.76	($p < 0.05$)
MET (sec)	7.1 ± 0.24	5.2 ± 0.16	($p = 0.07$)
FEF25-75/FVC	0.76 ± 0.33	1.03 ± 0.28	($p = 0.06$)
TLC (% predicted)	74 ± 12.32	79 ± 16.10	
RV (% predicted)	110 ± 26.47	107 ± 48.39	
FRC (% predicted)	72 ± 15.04	76 ± 29.31	

TLC = total lung capacity; RV = residual volume; FRC = functional residual capacity

Responders had a significantly reduced FEF25-75 % predicted. Regression analysis revealed that ln PC20 correlated with forced expiratory flow during the middle half of the forced vital capacity (FEF25-75) % predicted ® = 0.49; $p = 0.004$), maximum expiratory time (MET) ® = 0.45; $p = 0.01$) and forced expiratory volume in one second (FEV1) % predicted ® = 0.43; $p = 0.01$). These findings cannot be attributed to smoking among responders because PC20 values for current smokers (mean = 3.12 mg/mL) were comparable to those of never smokers (mean

= 1.71 mg/mL). Among responders, those who had a PC20 of < 2 mg/mL compared with those who had a PC20 > 2 mg/mL demonstrated a significantly lower forced vital capacity (FVC) (52 ± 13 vs 64 ± 15 % predicted; $p < 0.05$) and lower FEV1 (55 ± 13 vs 66 ± 15 % predicted; $p < 0.05$). These findings of decreased airway caliber assessed by FEF25-75 and FEV1 and reduced exchangeable lung volume, assessed by FVC, suggest that bronchial hyperresponsiveness may be due to stiff and noncompliant airways as a result of an inability to maximally stretch airway smooth muscle during deep inspiration.

A Prescription for Arm Exercise Using a Modified Target Heart Rate Training Range. J.M. Wecht[1], A.M. Spungen[2], D.R. Grimm[2], M. Strakhan[1], and W.A. Bauman[2]. [1]Spinal Cord Damage Resource Center and [2]Department of Medicine, Bronx VA Medical Center, Bronx, NY.

Introduction: Exercise training at intensities above the anaerobic threshold (AT) may lead to overtraining, and is often counterproductive. The best method for prescribing exercise is use of the AT heart rate (ATHR) determined from a maximal metabolic exercise stress test. This method however is not readily available to many facilities. As an alternative, one of two formulae are used to establish a target heart rate training zone for safety and optimal cardiopulmonary aerobic fitness improvement: World Health Organization [WHO = 210 - (age x 0.65) x 0.60 to 0.80] and Karvonen [KAR = (220 - age - resting HR) x 0.60 to 0.80 + resting HR]. Since both formulae were derived from weight-bearing leg exercise testing in an able-bodied population, they may not accurately reflect ATHR during arm exercise in those with spinal cord injury.

Objective: This study sought to compare ATHR determined from a metabolic arm exercise stress test with the mean calculated training ATHRs (±20%) from the WHO and KAR formulae.

Methods: Six healthy males with paraplegia completed a total of 15 maximal arm exercise stress tests. All subjects had a spinal lesion at or below the sixth thoracic vertebrae, were motor complete, and were at least 4 years post-injury. Analysis of variance was used to test for significant differences among the average calculated KAR and WHO training ATHRs (± 20%) and the metabolic ATHR measured from the maximal arm exercise test. Gas exchange analyses for oxygen consumption (VO_2) and carbon dioxide (VCO_2) production were measured by a metabolic cart (System 2900, SensorMedics Corp., Yorba Linda, CA). The metabolic ATHR was determined using the V-slope method from the regression of VCO_2 on VO_2 (Wasserman et al., Principles of exercise testing and interpretation. Philadelphia: Lea & Febiger; 1987).

Results: The mean calculated KAR and WHO training ATHRs (± 20%) were significantly higher than the average metabolic ATHR (± 20%) measured during the exercise stress test (154.5 ± 3.2 and 152.3 ± 3.4 vs 127.3 ± 16.3 bpm; $p < 0.05$). These results indicate that the standard formulae overestimate the subject's training HR by an average of 17% (range of 11–23%). Training at a level of 17% above AT is likely to result in noncompliance and is potentially dangerous. In order to provide a more appropriate and safe prescription for arm exercise training, the current formulae may be used, if modified by a multiplication factor of 0.83 {WHO = [210 - (age x 0.65) x 0.83] x 0.60 to 0.80 and KAR = [(220 - age) x 0.83 - resting HR] x 0.60 to 0.80 + resting HR}.

Conclusions: This modification for arm exercise training will help to maximize cardiopulmonary aerobic fitness gains and minimize potential deleterious effects.

Anabolic Agent Versus Anabolic Agent Combined with Inspiratory Muscle Training: The Effect on Lung Function in Individuals with Spinal Cord Injury. A.M. Spungen[1], D.R. Grimm[1], M. Strakhan[2], and W.A. Bauman[1]. [1]Department of Medicine and [2]Spinal Cord Damage Resource Center, Bronx VA Medical Center, Bronx, NY.

Introduction: Many individuals with tetraplegia have moderate to severe reductions in lung function, and 80% have self-reported symptoms of breathlessness (Spungen et al., 1997; 35:652–657). Any intervention to improve breathing would be beneficial. Resistive inspiratory muscle training (IMT) has been demonstrated to improve pulmonary function in persons with tetraplegia (Rutchik et al., Arch Phys Med Rehabil 1998; 79:293-297). Preliminary studies with a synthetic anabolic agent, oxandrolone (Oxandrin™, BTG, Corp., Iselin, NJ) have demonstrated an improvement in certain static pulmonary function parameters after one month of therapy in individuals with tetraplegia (Spungen et al., American Spinal Injury Association, 1998 Annual Meeting).

Objective: This investigation sought to determine the effect of oxandrolone therapy alone and the combined effect of oxandrolone therapy and resistive IMT on static pulmonary function in individuals with tetraplegia.

Methods: The study consisted of 2 randomly assigned groups: those who received oxandrolone therapy alone (Ox only) for 4 months, and those who received oxandrolone therapy for 2 months then oxandrolone therapy plus resistive IMT (Ox + IMT) for the next 2 months. For the variables studied, percent change from baseline was determined at months 2 and 3, and compared by one-sample analysis of variance (ANOVA). An unpaired T test was used to compare the percent change from baseline to month 3 between the two study groups.

Results: To date, 9 male subjects with tetraplegia (C4 – 7) have completed 3 months of the 4 month study. The age and duration of injury (mean ± SD) for the total group was 41 ± 10 yrs and 16 ± 8 yrs, respectively. After 2 months of Oxandrin therapy ($n = 9$), the mean percent increases were as follows: forced vital capacity (FVC), 10 ± 7.5, $p < 0.005$; forced expired volume in one second (FEV1), 10 ± 6.5, $p < 0.005$; peak expiratory flow 13 ± 11.0, $p < 0.01$; forced inspiratory vital capacity (FIVC), 15 ± 11.3, $p < 0.005$; maximum inspiratory pressure, 20 ± 22.4, $p < 0.05$; and maximum expiratory pressure, 17 ± 25.0, NS. After 1 month of resistive IMT (month 3 of study), the Ox + IMT group ($n = 5$) had significant additional improvements compared with the Ox only group for FVC (6.6%, $p < 0.05$) and FIVC (5.9%, $p < 0.05$) with a positive trend in the other lung function parameters.

Conclusions: The preliminary results appear to indicate a positive trend for pulmonary function improvement with oxandrolone therapy, with additional improvement gained from combined treatment with oxandrolone and resistive inspiratory muscle training.

Queens Hospital Center

Severe Gastroparesis and Small Intestinal Dysmotility in a Patient with Mixed Connective Tissue Disease. F. Ahmad, M. Khan, C. Saha, N. Abid, A. Opran, L. Kasturi, S. Chokhavatia, K. Chawla, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Gastrointestinal dysmotility occurs in 10 – 20% of systemic lupus erythematosus patients and includes dilatation of the esophagus, stomach, and megaduodenum. Gastrointestinal symptoms in Mixed Connective Tissue Disease (MCTD), which resemble those of Progressive Systemic Sclerosis, frequently (80%) lead to generalized gastrointestinal dysmotility. We present a case of MCTD whose clinical course was remarkable for precipitous worsening of intestinal motility over a 4-week period.

A 54-year-old Jamaican woman presented with a 3-week history of large volume watery diarrhea, bilious vomiting and mild generalized abdominal discomfort. There was no history of recent travel or ingestion of unusual food. No family member had similar symptoms. The patient denied rectal bleeding, fever, tenesmus and jaundice. The patient was dehydrated. Her abdomen was soft, flat and non-tender with no organomegaly and normal bowel sounds. Seronegative rheumatoid arthritis was diagnosed 3 years earlier because of morning stiffness of more than one hour, symmetrical arthritis of both wrists and proximal interphalangeal and shoulder joints, and Raynaud's phenomenon. While positive antinuclear antibody (ANA) titer was 1:32, rheumatoid factor, anti double stranded DNA and extractable nuclear antibodies (including anti Ro-SSA, anti LA-SSB, anti-Smith and anti-ribonucleoprotein antibodies) were negative. She denied photosensitivity, recurrent abortions, deep venous thrombosis, skin rashes, oral ulcers, and dryness of eyes or mouth.

At the onset of her gastrointestinal symptoms, she had positive titers for anti-ribonucleoprotein and anti-Smith antibodies. These markers had led to the diagnosis of MCTD with positive serology for systemic lupus erythematosus. Cryptosporidium was isolated from her stool and eradicated with paromomycin and azithromycin. However, the diarrhea persisted and did not respond to a short course of steroid treatment. Two weeks later, she developed abdominal distension without nausea, vomiting or abdominal pain. Radiographs confirmed megastomach and megaduodenum. Mechanical obstruction was ruled out by barium study, which showed gastroparesis, megastomach, megaduodenum and diffuse dilatation of the small intestine (Fig. 1). Erythromycin and metoclopramide failed to improve the gastrointestinal transit, as evidenced by continued abdominal distension and diarrhea. The diarrhea improved upon cessation of all oral intake. Continuous nasogastric suction relieved the abdominal distension. After 5 weeks, the patient developed pneumatosis intestinalis (Fig. 2), which was treated conservatively. Initially, she was maintained on parenteral nutrition. Four weeks later, she tolerated small liquid diets with cisapride.

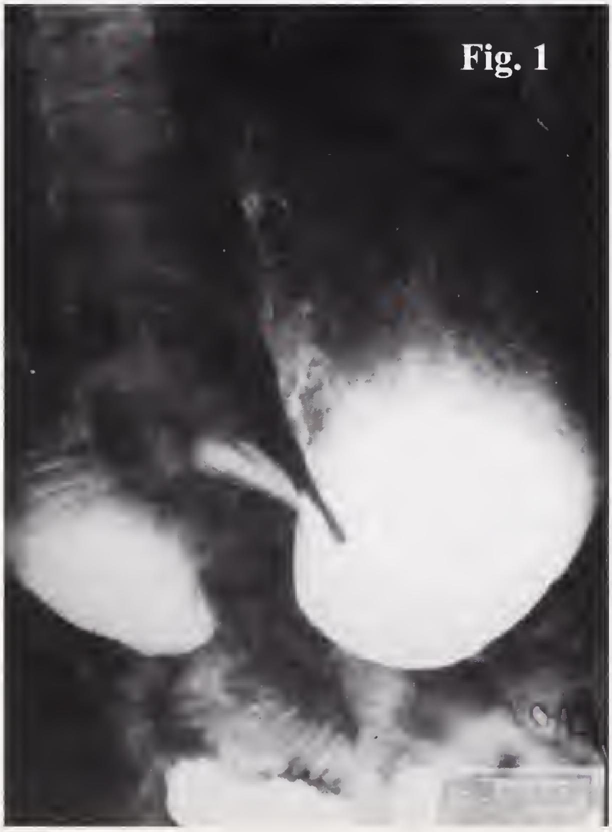


Fig. 1

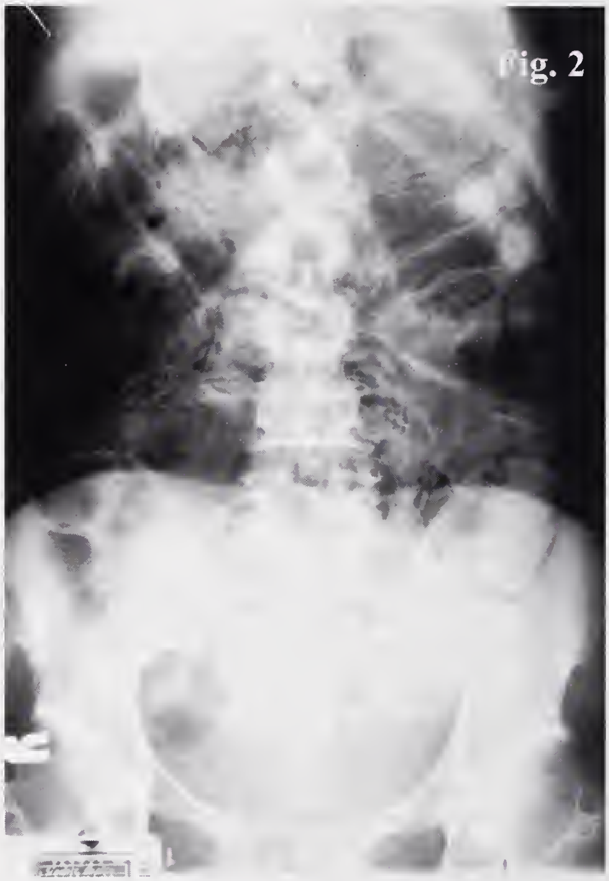


Fig. 2

Connective tissue diseases complicated by pneumatosis intestinalis forebodes poor prognosis. However, this complication should be recognized so that unnecessary surgery can be avoided.

* Submitted to the 63rd Annual Scientific Meeting of the American College of Gastroenterology, October 1998.

Marked Hyperlipidemia in an AIDS Patient Receiving Ritonavir Therapy. M. Chianurashvili, Z. Haque, I. Sachmechi, M. Johnson, S. Chokhavatia, and F. Rosner. Department of Internal Medicine, Mount Sinai Services at the Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Protease inhibitors provide significant clinical and survival benefits in HIV-infected patients. Insulin resistance, hyperlipidemia and abnormal liver function tests are recognized side effects of this class of drugs. We report an AIDS patient treated with Ritonavir, who developed marked hyperlipidemia.

A 44-year-old Hispanic man formerly known to be an alcoholic, was diagnosed with AIDS in 1996. He was evaluated for abdominal pain, nausea and vomiting. Ritonavir therapy had been started one year prior to this episode. On physical examination arcus senilis, tuberous xanthomas, lipemia retinalis, and hepatosplenomegaly were noted, but no xanthelasmas. The patient's serum appeared milky. There was marked elevation of serum triglycerides 1346 mg/dL (normal range - 55 – 122) and cholesterol 1067 mg/dL (150 – 210), as well as impaired liver function tests: aspartate aminotransferase 64 units/L (normal range - 20 – 40), alanine aminotransferase 87 units/L (2 – 50), alkaline phosphatase 161 units/L (30 – 115), gamma-glutamyl transpeptidase 1679 units/L (0–40), total protein 8.1 g/dL (6.5–8.5), albumin 4.7 g/dL (3.5–5.5), total bilirubin 1.7 mg/dL (0–1.5), conjugated bilirubin 0.5 mg/dL (0 3), and normal amylase and lipase. Five days after discontinuation of Ritonavir therapy, serum cholesterol decreased to 741 mg/dL and triglycerides to 896 mg/dL. Abdominal ultrasound showed hepatosplenomegaly with a normal pancreas and gallbladder.

The mechanism for marked hyperlipidemia with protease inhibitor therapy in HIV patients is not clear. The catalytic site of HIV protease inhibitor has a 70% homology with a low-density lipoprotein receptor-like protein (LRP), a hepatic scavenger of clearance of low density lipoproteins, resulting in accumulation of low density lipoproteins, intermediate density lipoproteins and very low density lipoproteins. Our recent survey of 100 patients with HIV infection or AIDS who are receiving protease inhibitors, revealed that 4% of these patients developed hyperlipidemia (unpublished observations).

We suggest that lipid profiles be routinely checked prior to and after initiation of protease inhibitor therapy so that the development of marked hyperlipidemia can be carefully assessed in these patients.

Clinical Vampirism in Modern Psychiatry: A Case Study with Psychoanalytic and Cultural/Historical Observations. B.S. Grube. Department of Psychiatry, Division of Psychology, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

The vampire has existed as a character in myth and folklore across virtually all cultures since antiquity, and more recently has emerged as a pervasive theme in modern television, cinema, literature, and even fashion. Occasionally, people exhibiting vampiristic behavior are identified as having a psychiatric disorder. We recently treated a young adult male on an inpatient psychiatric unit who presented with the delusional belief that he was a vampire. He had engaged in blood-drinking in various ways during this episode of psychosis and at different points throughout his life. Although the patient had two prior inpatient psychiatric hospitalizations, he apparently had not previously identified himself as a vampire, and he reported that this belief began after seeing a recent popular movie about vampires. He had begun to bite others following a period of physical abuse from a caretaker when he was a child. He also reported involvement in inappropriate sexual situations as a child, some of which involved exposure to menstrual blood. While this patient shared a number of important characteristics with other patients exhibiting clinical vampirism, including early separation from his mother, abuse as a child, and fascination with guns, his self-identification and manner of dress as a vampire were unique aspects of his presentation. This patient was diagnosed with schizophrenia and was treated successfully with neuroleptic medication and a range of psychotherapeutic interventions, resulting in his relinquishing the belief that he was a vampire.

The phenomenon of vampirism in clinical psychiatry, although rare, is not new, and a number of case studies have been well documented. These case reports, and other literature describing this phenomenon, underscore the richly symbolic nature of the acts committed by patients exhibiting clinical vampirism. While behavioral and symptomatic presentation varies widely, most cases (by definition) involve the ingestion of blood. In some cases of "auto-vampirism," patients imbibe their own blood. Most writers have emphasized psychoanalytic or other psychodynamic implications of vampiristic acts including: drive-based concepts of oral-aggression or sadism and primitive need-fulfilment; object-relations concepts of loss and fantasized preservation; Jungian concepts of a universal vampire archetype; and early-trauma concepts of re-enactment. The vampire's method of "stealing the soul" of his victim, or of transmitting his "illness," is sometimes viewed as a metaphor for the effects or transmission of child abuse. In addition, some writers have connected this phenomenon to certain diagnoses, especially paranoid schizophrenia and psychopathy, while others have even developed classification schemes based on subtypes of vampirism. While the emergence of delusion thinking is related to the onset of a schizophrenic episode, it is proposed that the particular content of the present patient's vampiristic self-identification and behavior can be understood as an interaction between psychodynamics following early traumatic experiences, including physical abuse, and later influences, including a cultural preoccupation with vampires.

Solitary Unilateral Renal Actinomycosis: A Brief Clinical Observation. A. Husain, C. Patel, E. Restrepo, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

A 29-year-old Guyanese man was hospitalized because of a 2-year history of left flank pain and intermittent fever. His appetite was poor and he had lost 22 pounds of weight. He denied urinary symptoms and trauma. There was no past surgical history. The man was cachectic, pale, febrile (101°F) and had a tender left costovertebral angle; however, there was no swelling or erythema. The patient had leucocytosis (12,800/mm^3) with 76% neutrophils, 15% lymphocytes, 7% monocytes and 2% eosinophils. Urinanalysis was unremarkable. Abdominal ultrasound revealed a left peripnephric mass. On abdominal CT scan, a mass infiltrating the left psoas muscle was seen arising from the left kidney. Percutaneous aspiration of the lesion under CT guidance yielded purulent material which contained Gram positive bacilli not further identified. The patient underwent abdominal laparotomy 2 days later. A large mass was found adherent to the left psoas muscle. The left kidney was mobilized off the left psoas muscle. There was marked perinephric induration, but no purulence in the retroperitoneal space. Malignancy was suspected and a left nephrectomy was performed. The kidney weighed 281 grams and a mass involved the upper pole. The surface was shaggy and irregular, containing multiple molecular areas with yellowish discoloration. The pelvicalyceal system, ureter and hilum were intact. Microscopically, multiple confluent areas with dense chronic inflammatory infiltrate and central abscess formation obliterated the renal parenchyma. The abscess cavity contained many basophilic bacterial colonies with radiating filamentous structures which were Gram positive but negative on acid-fast stain, diagnostic of actinomycosis. The patient was treated with penicillin G. His pain and fever subsided, the leucocytosis resolved, and the patient recovered fully. During the subsequent months he gained weight, had a good appetite and was asymptomatic.

Primary renal actinomycosis is a rare disease. Only 6 cases have been reported in the English literature since 1966. The diagnosis of renal actinomycosis is extremely difficult to make before nephrectomy. Even at surgery, it is hard to distinguish the lesion from a renal tumor. In most cases, a tumor, abscess or tuberculosis is suspected. Because of the difficulty in preoperative diagnosis, solitary renal actinomycosis is often managed by nephrectomy followed by antibiotic therapy. If the diagnosis can be made preoperatively or at operation, nephrectomy may not be necessary since prolonged antibiotic therapy alone may be curative.

Hypoglycemia Induced Ischemic Changes in a Patient with Normal Coronary Arteries. A. Husain, M. Raza, and F. Rosner. Department of Medicine, Division of Cardiology, Mount Sinai Services at Queens Hospital Center Jamaica, NY and the Mount Sinai School of Medicine, New York, NY.

A 43-year-old African American man with diabetes mellitus, who was known to have abused alcohol but not drugs, was found unconscious at home by ambulance personnel. He was given 100 mL 50% dextrose, following which he regained consciousness. His pulse rate was 84 beats/min and regular, and his blood pressure was 160/102 mm Hg. His blood sugar was 56 mg/dL. The only known risk factors for coronary artery disease were diabetes mellitus and male gender. The physical examination was normal. An ECG showed ST elevation and T wave inversion in leads V1 through V4 (Fig. 1). A prior ECG was completely normal (Fig. 2). In the emergency room, the patient complained of substernal pressure radiating to the left arm with diaphoresis. The patient was given intravenous nitroglycerin and heparin, and became asymptomatic. Three sets of cardiac enzymes, done at 8-hour intervals, were normal. Urine toxicology screen was negative for substance abuse. An ECG taken 3days later was normal. An adenosine stress test showed normal myocardial perfusion, and cardiac catheterization revealed normal coronary arteries.

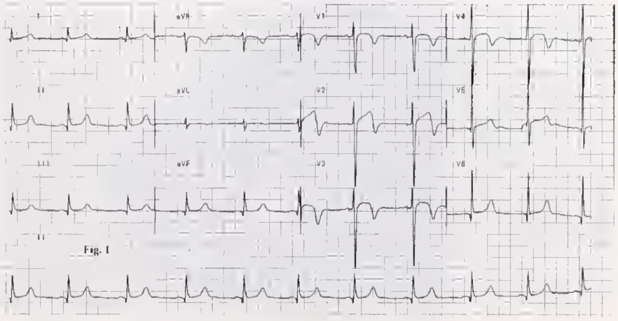


Fig. 1

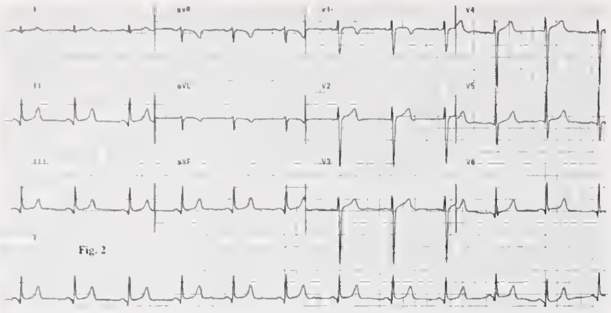
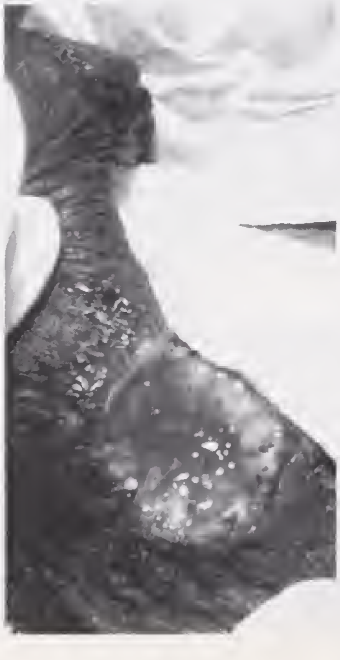


Fig. 2

Hypoglycemia induced ischemia in patients with coronary artery disease has been described previously as due to a sympathetic response, leading to an increased heart rate and blood pressure product, indicative of a supply and demand imbalance. However, anginal pain at rest, associated with ECG changes lasting 3 days and normal coronary arteries on angiogram, has not been described before. Although we have no conclusive explanation, possible mechanisms include sympathetic overactivity, decreased myocardial metabolic substrate availability, and endothelial dysfunction with vasomotor abnormality.

Recurrent Orogenital Ulcers in a Patient with Myelodysplastic Syndrome. S. Karuvannur, E. Lipstein, D.J. Brennessel, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

We report a 67-year-old man with Myelodysplastic Syndrome (MDS) who presented with painless penile (Fig.) and groin ulcers. He stated that "little" bumps appeared all over his body and disappeared on their own, occasionally breaking into small ulcers. He had no cardiovascular, respiratory, gastrointestinal or urinary complaints. He denied fever, chills, anorexia and loss of weight. He had a history of hypertension, insulin-requiring diabetes mellitus and peptic ulcer disease, and was taking captopril, isophane insulin suspension, regular insulin and sucralfate. He had received erythropoietin and filgrastim during the previous year for his MDS but had received no cytotoxic chemotherapy. He denied allergies, smoking, alcohol, drug abuse and sexually transmitted disease. The family history was noncontributory. On day 5 of hospitalization he developed fever of 103°F and 3 days later he developed oral ulcers. By day 17 he had severe odynophagia. Endoscopy showed severe esophageal ulcerations over a 15-cm length. Cases of Behçet's Syndrome and MDS have been reported in association with Trisomy 8 and HLA B51. Our patient had neither Trisomy 8 (searched for by fluorescent *in situ* hybridization) nor HLA B 51. Also lacking were other features typical for Behçet's Syndrome such as uveitis, vasculitis, central nervous system abnormalities and positive pathergy. The bone marrow karyotype had a normal male pattern and was consistent with chronic myelomonocytic leukemia. Biopsies of the oral and penile lesions were nonspecific. However, the orogenital and esophageal ulcers were exquisitely responsive to corticosteroids on the initial presentation and subsequent attacks.

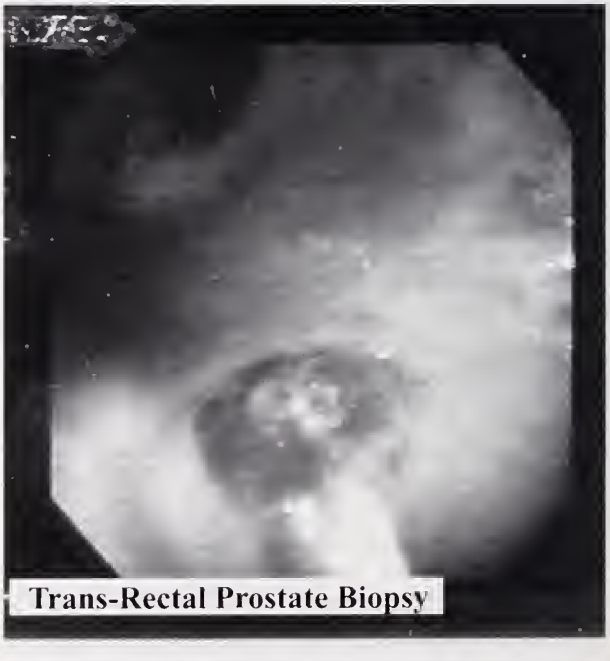


Photograph: Courtesy of C. Berman.

A Rare Cause of Gastrointestinal Hemorrhage: Transrectal Prostate Biopsy. L. Kasturi, C. Saha, R. Lind, Jr., S. Chokhavatia, and F. Rosner. Departments of Medicine and Surgery, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Transrectal prostate biopsies are routinely performed for the diagnosis of prostatic carcinoma. Complications which occur in about 3 – 10% of cases include bacteremia, bacteriuria, hematuria, urethral and ureteral injury, pelvic hematoma, pelvic abscess, urinary extravasation and, in rare cases, rectal bleeding. The incidence of rectal bleeding varies from 0.6 – 6.5 %. Rectal bleeding after rectal surgery or transrectal biopsy of the prostate is usually controlled by rectal packing or balloon tamponade with a large Foley catheter or thermocoagulation. We report a patient in whom injection therapy controlled severe rectal bleeding after transrectal prostate biopsy in which carcinoma in situ was found.

A 76-year-old African-American man underwent transrectal prostate biopsy for evaluation of a prostate specific antigen level of 12.7 u/L. He denied any prior rectal surgery. The patient had not been taking aspirin and had no evidence of coagulopathy. Three hours after the procedure, he became hypotensive and evacuated 500 mL of fresh blood per rectum. Flexible sigmoidoscopy revealed two puncture sites in the rectum, one with an actively bleeding visible vessel (Fig.). Hemostasis was achieved with submucosal injection of 5 mL of 1:10,000 epinephrine. The patient's hematocrit decreased from 33 to 23% and he was transfused with 6 units of packed red blood cells. Five days later, rectal bleeding recurred. Flexible sigmoidoscopy was repeated. The previously seen vessel was visible but was not bleeding actively. The vessel was injected with 4 mL of 1:10,000 epinephrine, and the patient's vital signs and hematocrit remained stable.



One hour post-injection therapy, the patient had a large bloody bowel movement and the two puncture sites in the rectum were surgically sutured. No active bleeding was noted intraoperatively and did not occur at any time during the next 3 months.

We are unaware of a reported case of rectal bleeding after transrectal prostate biopsy controlled by injection therapy. In our patient, who was bleeding actively at the time of sigmoidoscopy, hemostasis was achieved with 5.0 mL of 1:10,000 epinephrine. Thermocoagulation has not been proven to be superior to injection therapy nor has the combined modality of injection therapy and thermocoagulation. Surgical suturing remains the definitive therapy. This case emphasizes the fact that in patients presenting with rectal bleeding it is important to consider prior surgical procedures in the rectum, and to be aware that injection therapy which causes local vasoconstriction can be used to achieve hemostasis.

* Accepted for poster presentation at the 63rd Annual Scientific Meeting of the American College of Gastroenterology, October, 1998.

Pancreatic Adenocarcinoma Presenting as Acute Hepatitis. A. Khariton, H. Wazaz, B. Morel, R. Arreola, K. Chawla, L. Kasturi, S. Chokhavatia, and F. Rosner. Departments of Medicine and Surgery, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

The annual incidence in the United States of pancreatic adenocarcinoma (PA) is about 12 per 100,000. The prognosis is very poor due to its nonresectability at the time of diagnosis. Most patients present with painless jaundice and sometimes with abdominal pain and weight loss. A cholestatic picture is common in the blood, and increased serum CA 19-9 marker levels are found in 60–100% of resectable cases. We report a case of PA presenting with clinical features of acute viral hepatitis and marked elevation of aminotransferases.

A 51-year-old African (Ghanaian) woman presented complaining of 2 days of nausea, vomiting and jaundice. She denied fever, chills, weight loss, abdominal pain, pruritus, weakness, constipation and joint pain. There was no history of addiction to alcohol or cigarettes. Her only medication was felodipine 5 mg per day for hypertension. The patient's most recent trip to Ghana was 3 months earlier and was medically uneventful. On physical examination, the sclera were icteric and the liver was enlarged (total span 16 cm) but not tender.

The blood leukocyte count was 5,600/µL, hemoglobin 12.4 g/dL, hematocrit 36.2%, platelets 245,000/µL, mean corpuscular volume 94.4 fL, alanine aminotransferase 1058 units/L, aspartate aminotransferase 949 units/L, total bilirubin 9.7 mg/dL, direct bilirubin 6.7 mg/dL, alkaline phosphatase 419 units/L, gamma-glutamyl transpeptidase 1124 units/L, albumin 4.3 g/dL, prothrombin time 10.9 seconds, partial thromboplastin time 23.6 seconds, and CA 19-9 <15 units/mL. Serology was negative for acute hepatitis A, B, and C.

Abdominal ultrasound examination revealed hepatomegaly, dilated biliary ducts (common bile duct diameter of 2.0 cm), dilated gallbladder and enlarged head of the pancreas. CT scan did not confirm enlargement of the head of the pancreas. The patient underwent Endoscopic Retrograde Cholangio-Pancreatography. Smooth narrowing of the distal common bile duct and proximal dilation of the biliary system were noted. The common bile duct was stented. Cytology of its brushing did not show malignant cells. CT guided fine needle aspiration biopsy (sensitivity 80–90%) of the head of the pancreas failed to show malignant cells. CA 19-9 levels were in the normal range.

Despite the negative findings, a high suspicion for PA prompted exploratory laparotomy, where PA was confirmed. A modified Whipple's procedure was followed by an uneventful postoperative period. Histopathology confirmed PA of the head of the pancreas. One of 20 lymph nodes was positive for tumor cells.

This patient with PA is unique in that she presented with findings suggesting acute hepatitis. The correct diagnosis was made because of high suspicion for PA. Painless jaundice should always be extensively investigated and include exploratory laparotomy in doubtful situations. An aggressive evaluation of patients can help diagnose PA, cholangiocarcinoma and carcinoma of gallbladder at early treatable stages.

* Accepted for the 63rd Annual Scientific Meeting of American College of Gastroenterology, to be held in October 1998.

Adhesive Capsulitis of the Shoulder in Post Coronary Artery Bypass Graft Patients. H. Lin, N. Paddu, and C.B. Yui. Department of Physical Medicine and Rehabilitation, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Adhesive capsulitis (AC) or frozen shoulder is characterized clinically by the insidious onset of shoulder pain and progressive restriction in all directions of both active and passive Range of Motion (ROM) of the shoulder joint. Although most ACs are idiopathic, certain medical and surgical conditions predispose patients to the development of AC. Coronary artery bypass graft (CABG) surgery is one of the risk factors. We present 3 cases of AC in post-CABG patients who had no preexisting shoulder problems. All 3 patients who developed AC post-CABG presented to the Rehabilitation Clinic about 4 months to one year after the surgery and met the diagnostic criteria for Adhesive capsulitis. A combined treatment approach was used, which included the intraarticular injection of 1 cc (4 mg) of dexamethasone and 9 cc of 1% lidocaine, followed by manipulation of the shoulder complex, and having the patient attend an outpatient physical therapy program. All 3 patients had pain relief; 2 patients showed 90% restoration of ROM. It is important to recognize that frozen shoulder syndrome is one of the potential complications related to CABG surgery.

Post Intubation, Mechanical Ventilation, Quadriparesis Rehabilitation Issues: A Case Report. N. Paddu, and I. Okoronkwo. Department of Physical Medicine and Rehabilitation, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Prolonged paralysis following the use of Non-Depolarizing Neuromuscular Blocking Agents (NDNMBA), e.g., pancuronium, vecuronium, atricarium and/or large doses of steroids, has been described in patients who are on mechanical ventilation for prolonged periods of time. Neuromuscular blocking agents are chemically related to steroids, which cause toxic myopathy or neuromuscular junction dysfunction in these patients. The cause of paralysis is unknown, and there are no reports evaluating early rehabilitation intervention of these patients in an Intensive Care Unit (ICU) setting. We report a 49-year-old female with a 25-year history of asthma and 4 prior intubations who presented with acute asthma and needed intubation and mechanical ventilation. She received small doses of vecuronium and large doses of steroids and aminoglycosides for pneumonia. She developed quadriparesis with proximal muscle and respiratory muscle weakness, and weaning from the respirator was difficult. She was intubated for 9 days. An electromyogram showed a myopathic process, but her creatinine phosphokinase level was normal. With physical and occupational interventions in an ICU, she became fully independent in activities of daily living and ambulated with a cane in 6 weeks. To prevent recurrence of this prolonged paralysis, the patient was encouraged to avoid the use of NDNMBA and steroids, and to reduce the duration of dependency on mechanical ventilation. Rehabilitation issues, which include the recognition of this condition, evaluation, and treatment in ICU, may decrease the overall morbidity in these patients.

Incidence of Thyroid Carcinoma in Single Cold Nodules Compared to Cold Nodules of Multinodular Goiters. I. Sachmechi, A. Chernys, E. Miller, Z. Carroll, E. Kissin, and F. Rosner. Department of Medicine, Division of Endocrinology, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Thyroid nodules occur spontaneously in 4–15% of the adult population. The incidence of cancer in solitary thyroid nodules (SN) ranges between 2.7 and 33% whereas that in multinodular goiters (MNG) is 1.4–10%. We performed fine needle aspiration of cold nodules in 146 patients, 95 of whom (89 females [F] and 6 males [M]) had MNG. Their mean age was 51.4 years. The other 51 patients had SN (46 F, 5 M) with a mean age of 38.3 years. Of the 95 patients with MNG, 16 had abnormal cytologic findings and underwent surgical excision. Twelve of the patients undergoing surgery had thyroid malignancies (6 papillary, 3 follicular and 3 Hürthle cell). Of the 51 patients with SN, 8 had suspicious cytology and all 8 underwent surgical excision: 5 had thyroid cancer (3 papillary and 2 follicular). Four patients with papillary thyroid cancer (3 from MNG group and one from SN) had a prior history of exposure to radiation. The rate of malignancy in cold nodules in the MNG group was 12.63% as compared to 9.8% in the group with SN ($p = 0.79$). Within the MNG group, 25% of the thyroid malignancies were of the Hürthle cell type. These results differ slightly from previous reports. In our series, there was a higher incidence of thyroid malignancy in cold nodules of MNG as compared to SN. This finding might be due to selection criteria, because only cold nodules were biopsied and 4 patients had a history of radiation exposure.

We conclude that: (1) multinodularity of the goiter should not be considered a low risk of malignancy; (2) thyroid scan and fine needle aspiration of cold nodules are important diagnostic tools for the thorough evaluation of both solitary and MNG; and (3) the incidence of malignancy in cold nodules of MNG is not significantly different from that in SN.

Pravastatin (Pravachol) Short Term Efficacy and Safety in Type 2 Diabetes Mellitus. I. Sachmechi, N. Varatharajah, and P. Pathi. Department of Medicine, Division of Endocrinology, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Pravastatin is a 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitor which decreases cholesterol synthesis. It is safe, effective and well tolerated in the long-term treatment of primary hypercholesterolemia. We examined the efficacy and safety of 20 mg pravastatin daily in reducing total cholesterol and low density lipoprotein (LDL) in patients with secondary hyperlipidemia due to type 2 Diabetes Mellitus (DM).

Twenty-two patients with type 2 DM were enrolled in the study (14 women and 8 men, age range from 32–75 years). Lipid profiles, liver function tests, creatine phosphokinase (CPK) and hemoglobin A_1C (HbA_1C) levels were determined before, and 12 weeks after, initiation of pravastatin therapy. Two patients were excluded due to noncompliance and one patient due to muscle pain and increased CPK levels. The results in the 19 patients who completed the study are shown in the Table.

We conclude that short term pravastatin therapy is effective and safe in reducing total cholesterol and LDL. Although the changes in HDL and triglyceride values in patients with type 2 Diabetes Mellitus were suggestive of improvement, they did not reach statistical significance in the 12-week study.

TABLE

	Cholesterol mg/dL		LDL mg/dL		HDL mg/dL		Triglyceride mg/dL	
n=19	range	mean±S.E.	range	mean±S.E.	range	mean±S.E.	range	mean±S.E.
Control	206–382	(270.4 ± 42.5)	135–267	(188.5 ±3 5.2)	20–79	(44.2 ± 14.7)	69–465	(204.8 ± 109.2)
Post 12 weeks	173–326	(238.7 ± 35.9)	105–232	(157 ± 36.0)	31–73	(47.2 ± 13.7)	59–359	(173.4 ± 93.2)
p value	0.0003		0.0003		0.1906		0.0706	

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In the Teeth of the Evidence:

The Curious Case of Evidence-Based Medicine

Frank Davidoff , M.D.

Abstract

For a very long time, evidence from research has contributed to clinical decision making. Over the past 50 years, however, the nature of clinical research evidence has drastically changed compared with previous eras: its standards are higher, the tools for assembling and analyzing it are more powerful, and the context in which it is used is less authoritarian. The consequence has been a shift in both the concept and the practice of clinical decision making known as evidence-based medicine.

Evidence-based decisions, by definition, use the strongest available evidence, are often more quantitatively informed than decisions made in the traditional fashion; and sometimes run counter to expert opinion. The techniques of evidence-based medicine are also helpful in resolving conflicting opinions.

Evidence-based medicine did not simply appear in vacuo; its roots extend back at least as far as the great French Encyclopedia of the 18th century, and the subsequent work of Pierre Louis in Paris in the early 19th century. The power of the evidence-based approach has been enhanced in recent years by the development of the techniques of systematic review and meta-analysis. While this approach has its critics, we would all want the best available evidence used in making decisions about our care if we got sick. It is only fair that the patients under our care receive nothing less. **Key Words:** Evidence, decision making, authority.

Introduction

A curious concept is sweeping through the medical literature, the hospital floors, and the conference rooms: the concept of evidence-based medicine. Symposia and meetings are held on the subject; books are written about it (1, 2); there is even a journal by that name (3). While enthusiasts energetically promote and teach the concept, skeptics have wondered what all the fuss is about. After all, haven't doctors always relied on "the evidence"?

To be sure, evidence of one kind or another has always contributed to clinical decision making, but "evidence" is only one element out of many that go into such decisions. Fig. 1 shows a useful way to represent these various elements and the complexity of their interplay. Personal factors include all of the internal life experience of patients and doctors: their culture, upbringing, education, life circumstances; the whole, rich, endlessly varied, subjective lot. Rules and constraints are the external forces — social, legal, ethical, administrative — that constrain clinical decisions. And then there is "the evidence": objective, published, formal scientific information from research. With complexity like this, it is no wonder that every investigator who has looked at the question has found wide variation in clinical practices among doctors and across regions of the United States.

Why, and Why Now?

It seems then that the rise of evidence-based medicine does not represent the sudden appearance of a strange new element in clinical decision

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Based in part on a Grand Rounds presentation at the Mount Sinai School of Medicine, New York, NY, on March 11, 1997.

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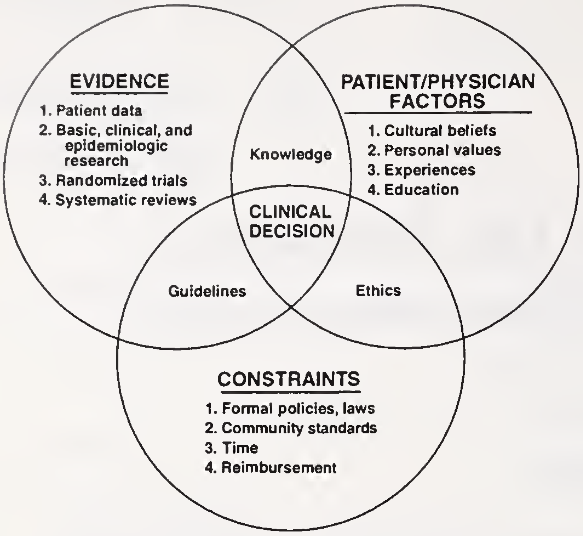

Fig. 1. Elements that enter into medical decisions.

making, but rather a shift in the balance among the existing elements, with greater weight now being put on "the evidence" than had been done in previous years. Yet if such a shift is taking place, the question is why? And why now? As I have suggested elsewhere, I believe it is happening because in the present "evidence era," which is to say roughly the past 50 years, at least three important things have changed (4). First, the standards for evidence have increased. Second, the quality and power of the tools for assembling evidence have improved, and those tools are much more widely available. And third, the social context in which evidence is used has changed.

The standards for evidence: Specifically, before the evidence era, the principal standard for clinical evidence was the case report, or the case series, which was largely observational and retrospective information. All good science begins with good observations, but observations serve largely to generate hypotheses rather than to confirm them. Now, in contrast, we have shifted to an epidemiological or group standard: the systematic recording of information, mostly quantitative, from groups or populations of patients.

The tools for assembling and analyzing the evidence: Before the evidence era, the tools for dealing with evidence were largely either descriptive statistics, or basic analytic techniques for manipulating and interpreting the numbers once assembled. Now, in contrast, we focus on the methods for obtaining the numbers in the first place: the increasingly sophisticated techniques of experimental design, mostly prospective, which include cohort studies, case control studies, and of course randomized controlled trials, the latter serving now as the "gold standard" for establishing the efficacy of interventions. Biostatistical concepts and techniques unheard of a few decades ago are now commonplace in the medical literature: decision analysis, test-operating characteristics, Bayesian analysis, receiver-operating characteristic curves, systematic reviews, meta-analysis, cost effectiveness analysis, the list goes on (5, 6).

As a historical note, the first randomized trial (on the efficacy of streptomycin in the treatment of tuberculosis) was published in 1948, a mere 50 years ago, just seven years before I entered medical school. In that short 50 years, about 131,000 randomized controlled trials of medical interventions have been published, although many more have been done but remain unpublished.

The other development that has fundamentally changed the tools available for handling evidence is, of course, the microcomputer. This technology, along with a variety of powerful statistical software packages, has put enormous statistical power onto the desk of every clinical investigator who cares to have it. As recently as 20 years ago, this kind of statistical power was available only on huge mainframe computers, jealously presided over by statisticians; prior to 20 years ago, it was hardly available at all.

The social context in which evidence is used: Before the evidence era, the social and cultural environment in which medical decisions were made was governed largely by expert opinion; medical thinking, teaching, and practice were all dominated by knowledge handed down from "the authorities," causing some to refer to this earlier time as the era of "authoritarian medicine." Now, in contrast, we have shifted increasingly to the expectation that every doctor will use "the evidence" for him or herself, and will rely progressively less heavily on the voice of authority. This change might be thought of as a shift from "authoritarian" to "authoritative" medicine or a "democratization of medical decision-making" (4).

A variety of changes in the larger environment have supported this intellectual and social shift. For one thing, government and industry are now paying enormous amounts for medical care and, not surprisingly, they are increasingly interested in knowing that they are getting value for their money. It may not be entirely accidental that some of the earliest development of strong experimental designs took place in Great Britain shortly after its National Health Service began to pay for all medical care. For another thing, the public and patients ask questions in ways they did not do 50 years ago, and they increasingly expect their doctors to give them "the evidence." Nowadays, of course, if doctors will not provide the evidence, many patients and their families simply look for it on the Internet. Last but not least, the courts increasingly want to hear "the medical evidence," not just medical opinion.

Evidence-Based Medicine: An Academic Discipline or an Approach to Clinical Practice?

So much for what has happened to the evidence itself. But is evidence-based medicine just a new concept, another of the many imaginative constructs that circulate from time to time in academe? Or is there such a thing as the "practice" of evidence-based medicine, a concrete discipline that can be taught, learned, and applied in daily practice out in the trenches? The answer might be that even though it began as a concept in academic centers, a real-world practice of evidence-based medicine is actually beginning to emerge. Many principles of this discipline, along with the underlying concepts and even the name, were developed at McMaster University Medical School in Hamilton, Ontario during the last decade or so. Indeed, many of the authors of the article, published in 1992, that first articulated the principles of evidence-based medicine, both as a concept and a practice, were from that school (7).

Even in these short 5–6 years, the principles and practices of evidence-based medicine have undergone considerable evolution. In 1995, Brian Haynes, one of the originators of the concept, provided this excellent, updated definition of the concept:

> *"The judicious and conscientious use of current best evidence from research, in making decisions about the health care of individuals and populations."*

The practice of evidence-based medicine rests on four basic steps. Like most good concepts, these steps are simple, but at the same time reflect a deep understanding of the nature of clinical learning. They are triggered when a patient presents a problem you do not understand, or a management situation in which the decision is not clear. They are as follows:

1. **Formulate** a clear clinical question from that problem or ambiguous situation.
2. **Search** for the relevant information from the best possible published (and, sometimes, unpublished) sources.
3. **Evaluate** that evidence for its validity and usefulness (that is, critically appraise it).
4. **Implement** the findings in your practice.

A specific example, taken from a very helpful 1995 article on evidence-based medicine (8), may help here. A patient, new to you, is admitted to your service. A 77-year-old woman who lives alone enters with her first bout of mild congestive failure, which is associated with non-rheumatic atrial fibrillation. Her history is remarkable only for moderate hypertension which has been fairly well controlled. An echocardiogram reveals moderately impaired left ventricular function. She responds well to digitalization and diuretics, but remains in atrial fibrillation. A debate now takes place (on rounds, with your colleagues, or in your head), as follows.

On the one hand, since her atrial fibrillation puts her at considerable risk for an embolic stroke, anticoagulation with warfarin seems to be the appropriate intervention. But on the other hand, the benefits and risks of long-term warfarin therapy relative to bleeding risk in this patient are not clear. How should you decide? Accept a trusted colleague's opinion? Go by the local standard of practice? Turn to the advice from a helpful drug detail man? Use what you read in a recent "throwaway?" Depend on your own experience with other such patients? Listen to the patient's preference? Pick up the phone and call Eugene Braunwald? Or practice evidence-based medicine? If you choose the latter, you might proceed as follows.

Formulate. In formulating the problem, you might convert the debate into two related questions:

- What is the baseline (untreated) risk of embolization in a patient of this age and clinical circumstance if not anticoagulated?
- How much is the risk for stroke reduced by warfarin therapy and, conversely, what is the risk of harming her with this therapy?

At this point, it is worth noting that the skeptics claim that evidence-based medicine has contributed little to the difficult problem of formulating (or "setting") clinical problems, that is, teasing out the "real" nature of the problem from the "messy" information served up by patients (9). These critics suggest that the discipline is primarily useful in solving problems after they have been well-formulated. To a degree, they are right: extracting information from a patient, and formulating a patient's problems well, are still not well-developed aspects of clinical problem solving (10). Yet in fairness, the developers of evidence-based medicine have put together some very useful approaches to setting up good, answerable clinical questions, for example, by designating the four elements of a well-formulated question (1). Besides, the originators of the concept have never pretended that evidence-based medicine could be all things to all people.

Search. An actual MEDLINE search was carried out on our patient's problem (8). It produced seven acceptable articles: two on prognosis, four on therapy, and one review (a meta-analysis); it took 15 minutes (and probably cost about $5 at the time; it would now be free).

Evaluate. Critical appraisal of research evidence involves applying explicit criteria of quality to research papers; it is an extraordinarily important subject, indeed a subject in itself, and goes well beyond the scope of this article. In brief, however, the criteria are mostly methodological, and are designed to determine the strength of the evidence that, in turn, allows you to ferret out the "strongest" evidence available on the clinical question at hand. Applying appropriate criteria, the following data were extracted from the retrieved literature.

- For these patients, the risk of embolic stroke, if untreated with warfarin, is about 18% per year.
- With anticoagulation, the relative risk for embolization is reduced by about 70%.
- The absolute risk reduction is thus 13 percentage points — from 18% down to 5%.
- From these figures, you can calculate the number of patients you would need to anticoagulate for one year to prevent one stroke, the so-called "number-needed-to-treat," or NNT, which in this case is about 8.

On the other hand, the annual rate of a major bleeding episode in such a patient on warfarin therapy is about 1%.

- The number of patients you would need to anticoagulate for a year to produce one major bleeding complication (the "number-needed-to-harm" or NNH) is about 100.
- Thus, by combining the two estimates, you find that in a year of treatment, you can prevent 13 strokes for every major bleeding event you cause.

What can you conclude from this example of evidence-based practice? How is it different from more "traditional" practice? What, if anything, are its unique contributions to patient care?

First, by definition, the practice of evidence-based medicine always connects you to the best, most complete, highest quality, most up-to-date evidence there is on a subject — once you get good at it and if you have the time, that is! Second, evidence-based practice is often more exact, more quantitative. That is, the answers may be qualitatively the same as if you had followed the more traditional approach, but with evidence-based medicine, they are often more quantitative, hence more sharply focused. Third, and importantly, evidence-based practice sometimes produces sound decisions that run counter to the conventional wisdom. Indeed, evidence-based decisions are not always consistent with expert opinion, since the experience of any one expert, however great, can only extend so far, and expert opinion can be highly idiosyncratic, or even wrong. And sometimes, evidence-based practice is helpful in resolving conflicting opinions, which inevitably occur in clinical medicine, and fairly frequently at that.

The Roots of Evidence-Based Medicine

As we have seen, the shift in the quantity and quality of "the evidence" over the past 50 years seems to have led up to a recent, and quite abrupt, formalization of this shift, and to its labeling as "evidence-based medicine." Nevertheless, changes like these do not occur in a vacuum; they generally arise from the coming together of forces that have been with us in one form or another for a long time. Just how old are the forebears of evidence-based medicine, and where did the first stirrings happen?

We can already detect the roots of such intellectual upheaval in the 18th century. For it was in that century, more specifically in the year 1751, that the first volumes of the great Encyclopedia were published in France (11). The first edition of this monumental, multi-volume work took some 20 years to assemble. Prepared under the editorship of a man of letters, Denis Diderot, and a mathematician, Jean d'Alembert, it contained some 71,818 articles, written by more than 300 scholars (15% of whom were doctors). The articles were arranged alphabetically in 17 volumes, accompanied by an additional 11 volumes containing the 2,885 illustrative plates.

Encyclopedias had been published before this one, particularly in England. However, the feature that distinguished the French undertaking was its Baconian approach. That is, the editors insisted on accurate, direct investigation of the phenomena of the world: investigating, looking and reporting first hand took precedence over ancient and officially approved dogma, authority, and tradition. The effect was electric, and several early attempts to publish the Encyclopedia were suppressed by the royal and ecclesiastical authorities before it finally saw the light of day.

It can hardly be an accident, therefore, that the first formal application of "the evidence" (in the modern sense) in medicine took place in France in 1836, just four years after the last edition of the great Encyclopedia, in 229 volumes, was published. The study in question was the extraordinary work by Pierre Louis on the effect of bloodletting on the course of pneumonia. Louis based his conclusions on thousands of observations that he made personally on the medical wards and in the autopsy room (12). His question was simple: Is bloodletting effective in the treatment of pneumonia? His experimental rationale was equally simple. Reasoning that if bloodletting truly worked, the illness should be shorter when a phlebotomy was performed early in its course rather than later, Louis set about collecting first-hand numerical data on the timing of the phlebotomy and the length of the illness.

The data clearly demonstrated the absence of any meaningful relationship between the timing of bleeding and the duration of pneumonia. Contrary to prevailing belief and practice, then, his study clearly failed to support any demonstrable therapeutic efficacy for bleeding. The work was immediately translated into English; both his results and, particularly, his methods had enormous influence on the development of scientific medicine in the United States and throughout the rest of the world.

Leap ahead now to 1956, the early days of the modern evidence era, some 120 years after the publication of Louis's work. Dr. David Seegal, one of the great clinical teachers at the Columbia University College of Physicians and Surgeons (P&S), puts the following mysterious formula on the blackboard at the end of a session in his introductory course for medical students on the clinical method:

$$WD_{LB} + LU_{BB} = K$$

After letting the students puzzle unsuccessfully over this for a while, Seegal explains what it means: When you come across something about a patient you don't understand, write it down in the Little Book [the equivalent of "formulate, and save, the question"], then look it up in the Big Book [the equivalent of "carry out a search"]. The result is knowledge.

Although Seegal did not include the critical appraisal and implementation steps, he had clearly captured the initial sequence in the practice of evidence-based medicine long before that practice had a name. For Seegal and all the rest of us at P&S, the "Big Book" was, of course, Cecil and Loeb's textbook of medicine (Robert Loeb then being the distinguished professor and department chair); we never dreamed of the kind of information richness available to us now. This brings us to the following question: If there is so much high-quality information (research evidence) now available out there, why are we not using the best research-based information in the world for every clinical decision?

Evidence-Based Medicine Today: The State of the Art

At least part of the answer may be that, first, that information is widely scattered all over the medical literature. Second, even if you do manage to get your hands on all the information on the topic you are looking for, it is hard to know about its quality. In sum, our medical knowledge system is highly chaotic — full of entropy (13) — with the result that we are starving for information in the midst of plenty. To provide proper support for the practice of evidence-based medicine, what we need, therefore, are new and better ways to bring order out of this information chaos. Certainly, the development of Index Medicus and its electronic version, MEDLINE, have been giant steps forward in this regard. Nevertheless, for all the speed and power of these information access tools, the retrieval, filtering, synthesis, and distribution of high-quality clinical research information are still difficult, frustrating, and time-consuming exercises.

Many important efforts designed to take us beyond these difficulties are now underway, but among the most remarkable of these is the Cochrane Collaboration. It started with a remarkable man, Archibald (Archie) Cochrane, an epidemiologist for the British National Health Services who did his major work in the 1950s and 60s, mostly in Wales. Among his other contributions, Cochrane conducted some of the early randomized trials of therapies, and was an early champion of the randomized trial. Recall that this was only a few years after the first randomized controlled trial in medicine was published.

But in addition to being ahead of his time, Cochrane thought big. For although he recognized the power of the individual clinical trial as a potent method for obtaining unbiased information on efficacy, he also recognized that the power of the individual trial was necessarily limited, because any single trial is such a limited sample of a complex reality. Reflecting on this problem in 1979, he said, "It is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials."

This widely quoted statement has served as the principal driving force for the creation of the collaboration that now bears his name. Cochrane was saying, in effect, that an individual trial may be "the truth" about a specific clinical question but it is rarely "the whole truth," and when it comes to clinical decision-making, it is the whole truth that we are really interested in. The statement was probably also the first clear description of the "systematic review" as a better way of getting at the whole truth (14). As the technique of carrying out systematic reviews has evolved over the past decade, the essential characteristics of these reviews have become clear, as follows: The first, and most important, requirement is that the search for all high-quality evidence, published and unpublished, must be exhaustive. Second, criteria for defining methodologic quality must be established beforehand and rigorously applied in selecting studies for inclusion in the review. Third, data must be extracted systematically, and the results expressed clearly.

It is important at this point to make a clear distinction between a systematic review and a meta-analysis. A systematic review is essentially an instrument designed to minimize bias in the retrieval of data; there is no requirement that the data be combined in any formal way. A meta-analysis, in contrast, is essentially a statistical technique for formal combination of the numerical results from multiple studies. Note that a meta-analysis can be carried out using a highly skewed or biased data set. More generally, therefore, while meta-analysis can contribute to the power of a systematic review, a meta-analysis is only as strong as the data assembled as its "substrate."

The power of systematic reviews is expressed best in the now well-known study of the efficacy of thrombolysis in myocardial infarction, published some years ago (15). As shown in Fig. 2, the authors assembled the results of some 33 randomized controlled trials, published between 1959 and 1988, that examined the efficacy of thrombolysis in reducing acute mortality. When

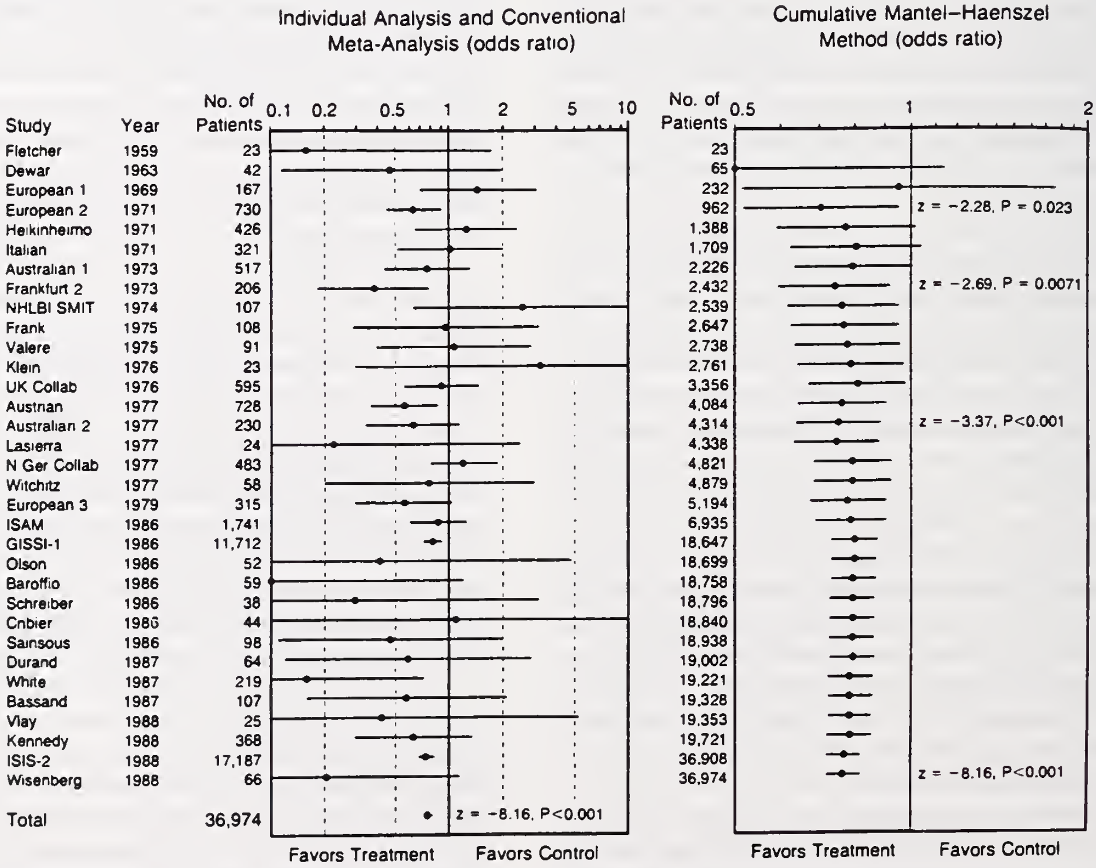

Fig. 2. Systematic review and conventional meta-analysis of 33 trials of intravenous streptokinase for acute myocardial infarction (left), and cumulative meta-analysis of the same trials (right). Odds ratios and 95% confidence intervals for the effect of treatment on mortality are shown on a logarithmic scale. (Reproduced with permission from Lau J, Antman EM, Jimenez-Silva J, et al., Cumulative meta-analysis of therapeutic trials for myocardial infarction. N Engl J Med 1992; 327:248–254.)

the results of the individual trials identified in this exhaustive search are laid out along a timeline, as shown in the left-hand portion of Fig. 2, several things become obvious. On the one hand, most of these studies do in fact suggest some benefit (lowered mortality in the thrombolysis group), although the confidence intervals in most studies overlap 1.0, which is also consistent with no true effect. On the other hand, the outcomes vary substantially from study to study; that is, despite the considerable power of the individual randomized controlled trial, there is still a good deal of "noise" in the system. Taken together, the results of these trials, when assembled in this systematic review, are suggestive; unfortunately, simply looking at this informal aggregation of results leaves considerable doubt about the size, and even the existence, of a therapeutic effect.

When, however, the results of these trials are formally and cumulatively combined, that is, trial two with trial one, then three with the first two, etc., as in the right-hand portion of Fig. 2 (a cumulative meta-analysis), it becomes immediately obvious that: by 1971, the therapeutic efficacy of thrombolysis was already statistically significant at the 0.05 level; by 1973, the level of significance reached 0.01; and by 1977, it increased further to < 0.001. Note also that in this cumulative analysis the GISSI trial, reported in 1986, and by far the largest study in the group, had very little effect on the point estimate of efficacy. All it did was to shrink the confidence interval slightly.

Despite this powerful evidence, the therapeutic efficacy of thrombolytic therapy was not fully recognized for decades; the chaos in the medical information system (or non-system) kept it hidden. Indeed, as recently as the early 1990s, some medical textbooks still included statements to the effect that thrombolysis was an unproved therapy. It is sobering to think about the many patients who could have benefitted from thrombolytic therapy but who did not, because our clinical research enterprise outran our ability to process and use the information it produced. It is almost as sobering to think about the precious research resources used unnecessarily to study an intervention whose efficacy had been established years, even decades, before — if only we had been smart enough to realize it.

The first serious effort to take up Cochrane's challenge to organize "critical summaries" was made in Oxford, in the United Kingdom. Led by an obstetrician, Iain Chalmers, a group of researchers there identified some 700 therapeutic interventions used during pregnancy and childbirth. From all the high-quality randomized controlled trials available at the time, published and unpublished, they synthesized the evidence concerning the outcomes of those interventions. As part of this effort, they sent out 40,000 letters to obstetricians around the world to obtain as much data as possible from unpublished trials. The result was the Oxford Database of Perinatal Trials, which was published initially as a massive, two-volume reference work (16). The principal findings were published soon after that as a small paperback volume that has been a worldwide best seller and is used extensively in training programs, health policy planning, and the like (17).

This initial Herculean effort subsequently evolved into the present-day Cochrane Collaboration (18, 19). The Collaboration Logo (Fig. 3) at first glance might be taken for simply another piece of modern graphic design. Those familiar with the technique will recognize it immediately, however, as a stylized version of the results from a systematic review. In fact, it displays the results of the 7 trials that established the efficacy of corticosteroids in preventing the neonatal respiratory distress syndrome, another example of an important therapy whose efficacy was not recognized for at least 10 years after ample evidence of efficacy was available (19).

The Cochrane Collaboration has already developed a worldwide network of centers, each responsible for setting up and supporting so-called "review groups." For reasons that are not entirely clear, the clinical research community in the United States has been relatively slow to become involved in the work of the Collaboration. However, the recent decision of

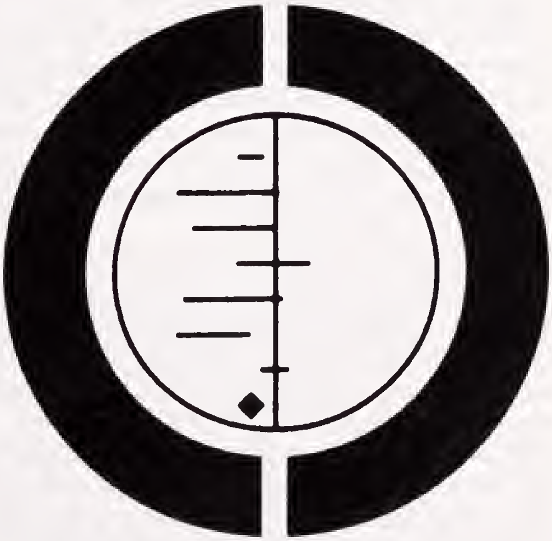

Fig. 3. The logo of the Cochrane Collaboration.

the Federal Agency for Health Care Policy and Research to fund 12 evidence-based practice centers, which include all of the U.S. Cochrane Centers, may reflect a change in this nation's perspective. The purpose of the review groups, and the Collaboration as a whole, is to produce, maintain, update, and distribute systematic reviews of high-quality evidence in as many areas of medicine as possible. The Collaboration held its sixth international colloquium, attended by more than 700 researchers, in Baltimore in the fall of 1998.

More than 3,000 health professionals are now involved in the work of the Collaboration. Importantly, consumers have been systematically included in the effort, helping to set priorities, interpret findings, and disseminate results. As of the fall of 1997, the Collaboration had already produced close to 250 systematic reviews of its own, which are published and updated electronically, and many other reviews are underway under its aegis (20). It is estimated that more than 1,600 non-Cochrane systematic reviews have been published. The Collaboration also maintains an international registry of randomized controlled trials.

Looking Ahead

Writing in the 1600s, Sir Francis Bacon could have been thinking of the present-day practitioners of evidence-based medicine when he predicted that an assemblage of scholars would engage in an "admirable conspiracy" to flood with light the world of the arts and sciences (11). He was also prescient in envisioning that "Then will arise, from the dark realm of the sophists and the envious, a dark swarm which, seeing these eagles soaring and being unable either to stop or to follow their rapid flight, will try by their vain croakings to belittle their accomplishment and their triumph." Indeed, while it is unlikely that its developers and practitioners see themselves as either an admirable conspiracy or soaring eagles, the critics of evidence-based medicine have not been slow to come forward.

They cite a number of concerns, most frequently the following. First, they worry about the seeming obsession with randomized controlled trials, to the exclusion of evidence of other kinds, e.g., observational studies, case-control studies, cohort studies, and the like (21). Second, they emphasize that while the results of controlled trials ("efficacy studies") may in fact be valid under rigorous trial conditions, those conditions are highly artificial; applying the same interventions in the messy world of everyday reality may not produce the same beneficial, and harmful, effects. (Intervention studies conducted under real-world conditions are known as "effectiveness studies.") Third, they describe the difficulty of applying the results of even valid controlled trials to individual real patients, since real patients, with all their comorbidities and risk factors, frequently differ from the carefully selected subjects of controlled studies. Fourth, they point out that most clinical questions for which practitioners need answers will never be answered by formal clinical research, because the resources to do so will never be available, and because the questions themselves continuously change. Fifth, they complain, bitterly at times, that the enormous body of clinical experience, the clinical wisdom amassed by expert clinicians, may often be ignored or even denigrated during the "worship" of formal research evidence (9, 22). Finally, they even complain about the name "evidence-based medicine," since as noted above, it seems to imply that doctors who do not adopt this "elite" approach do not use evidence in their decision making. Brian Haynes recently reflected, rather wistfully, that it might have been better right from the beginning to have called this approach "evidence in support of practice."

Although the evidence-based medicine "movement," like all intellectual movements, has spawned its share of zealots, its originators and most of those who actively support it agree that the concerns raised by the critics are generally quite appropriate. Moreover, most of its proponents understand very clearly that evidence-based medicine, like any other medical technique, does not provide magic solutions; that it was never meant in any sense to "replace" clinical experience. On the contrary, clinical experience is what provides the context for and gives meaning to "the evidence." Nevertheless, the proponents of evidence-based medicine would also argue that the research-oriented approach embodied in evidence-based medicine does add something important. They maintain that the evidence available now is vastly more abundant and enormously stronger than what was available even 40–50 years ago. They are deeply impressed that "the evidence" can inform, refine, sharpen, enrich, and enhance clinical experience.

Perhaps the ultimate criterion for judging the contribution of evidence-based medicine, however, is for each of us to consider what we will want for ourselves when we get sick. We will probably not want anything less than the best evidence the entire world has to offer. It is only fair, therefore, to ask why we should settle for anything less in making clinical decisions for, and with, the patients under our care.

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DNA Vaccines for Prophylactic or Therapeutic Immunization Against Hepatitis B Virus

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Abstract

DNA vaccines, with which the antigen is synthesized *in vivo* after direct introduction of its encoding sequences, offer a unique method of immunization that may overcome many of the deficits of traditional antigen-based vaccines. By virtue of the sustained *in vivo* antigen synthesis and the comprised stimulatory CpG motifs, plasmid DNA vaccines appear to induce strong and long-lasting humoral (antibodies) and cell-mediated (T-help, other cytokine functions and cytotoxic T-cells) immune responses. In animal models, DNA vaccines against hepatitis B virus (HBV) give humoral and cell-mediated immunity superior to that of the current traditional antigen-based vaccines, indicating the possibility of a more effective prophylactic vaccine against HBV. Furthermore, DNA vaccines can overcome tolerance to and expression of HBV proteins in a transgenic mouse model of the HBV chronic carrier, opening up the possibility of an effective therapeutic DNA vaccine to treat chronic carriers of HBV. **Key Words:** DNA vaccine, hepatitis B, immunotherapy, antibody, cytotoxic T-lymphocyte.

What Is a DNA Vaccine?

Traditional vaccines against infectious diseases involve administration of some form of the pathogen itself. This can be either the whole pathogen in a killed (e.g., by treatment with formaldehyde or heat) or attenuated (i.e., rendered nonpathogenic through growth under abnormal conditions or genetic alteration) form. Alternatively, the vaccine may comprise a subunit of the pathogen, such as the envelope protein used in the current vaccines against the hepatitis B virus (HBV). Such subunit vaccines may be purified (e.g., from the plasma of HBV chronically infected individuals) or produced artificially in cell lines as a recombinant protein (e.g., the current HBV vaccine from yeast cells).

In contrast to the traditional antigen-based vaccines, DNA vaccines involve introduction of plasmid DNA encoding the antigen. A plasmid is a double-stranded, closed circular form of DNA that can be produced easily in bacteria and then purified by chromatography. Upon injection into the body, some of the DNA enters cells of the body, where it enters the nucleus and, without integration into the genome, uses the cell's machinery to direct synthesis of the encoded antigenic protein. Since the body makes the antigen itself, it is in a sense its own vaccine factory.

The gene incorporated into the DNA vaccine can encode one or more complete proteins, or alternatively, only a portion of a protein that contains B- and/or T-cell epitopes. Since one can easily choose which genes or parts of genes to include, it is possible to exclude any gene related to virulence or toxicity. In addition to antigen-

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encoding sequences, DNA vaccines also contain genetic elements that permit or facilitate growth of the plasmid in bacteria (e.g., a bacterial origin of replication to allow amplification of large quantities of plasmid DNA in bacteria, and a prokaryotic selectable marker gene such as an antibiotic resistance gene to ensure that only bacteria containing the plasmid can survive and divide in culture). In addition, DNA vaccines permit expression of the antigen in the body (e.g., promoter and enhancer sequences to drive transcription and a transcription termination element to ensure appropriate termination of the expressed mRNA and polyadenylation).

Why Do We Need New and Better Vaccines?

What Is the Goal of Vaccination?

The goal of vaccination is to induce immune responses against components of the pathogen, so that infection or disease will be prevented or attenuated if the real pathogen is encountered. Two general types of immunity may be induced in response to an antigen, namely humoral immunity (the production of antibodies) and cell-mediated immunity (CMI), which involves a number of different cellular responses.

Antigen-specific antibodies are produced by B-cells that recognize and bind circulating, soluble antigen via surface antibody receptors. This process alone results in secretion of T-independent antibody isotypes (IgM and IgG3). However, for induction of the longer-lasting, high affinity T-dependent antibodies (e.g., IgG1, IgG2a), B-cells must be further stimulated by cytokines secreted from activated T-helper (T_h) cells (see below). Some activated B-cells become plasma cells that provide long-term memory.

CMI is the result of activated T-cells that recognize short segments of antigen (peptides) presented on cell surfaces via molecules encoded by the major histocompatibility complex of genes (MHC). Class I MHC presentation occurs on any nucleated cell in which there is endogenous synthesis of an antigen (e.g., infected cells). Some T-cells (usually CD8+) are activated by such MHC-class I antigen-presenting cells to differentiate into cytotoxic T-lymphocytes (CTL), although the influence of cytokines secreted by T_h cells is required for them to be fully potent. CTL can act on infected cells presenting antigen by class I MHC by both cytolytic mechanisms (e.g., secretion of perforin, which puts holes into the cell membrane) and non-cytolytic mechanisms (e.g., secretion of cytokines that prevent virus replication).

Other T-cells (usually CD4+) are activated to become T_h cells by recognizing antigen presented on class II MHC molecules that are found exclusively on professional antigen-presenting cells (APCs) such as macrophages and dendritic cells. T_h cells secrete cytokines and are of two basic types. T_h1 cytokines (e.g., IL-2, IFN-γ, IL-12) stimulate both CTL and B-cells, while T_h2 cytokines (e.g., IL-4, IL-5, IL-10) act predominantly on B-cells. T_h1 cytokines can also have direct effects on viral replication or assembly (1, 2).

Ideally, a vaccine will safely induce both antibodies and CMI. While humoral immunity alone is sufficient for prophylaxis against some diseases (e.g., HBV), CTL are still desirable and are absolutely essential for many diseases. In particular, treatment of chronic infections such as HBV requires CMI.

What Are the Shortcomings of Current Antigen-Based Vaccines?

Vaccines containing a live pathogen, either an attenuated (e.g., hepatitis A vaccine) or related but less virulent (e.g., vaccinia for smallpox) version of the virulent strain, are usually highly effective at inducing a full range of immune responses by virtue of the intracellular synthesis of antigen with the controlled "infection." The major disadvantage of these vaccines is the possibility of reversion to a virulent form, especially in immunocompromised individuals (e.g., neonates, HIV-infected or malnourished individuals). In addition, not all pathogens may be attenuated (3).

On the other hand, whole-killed or subunit vaccines do not induce intracellular synthesis of antigen, and because of this there is poor or absent presentation of antigen on class I MHC, and thus poor induction of a CTL response. CMI may be further compromised when the vaccine is administered with an adjuvant. Aluminum hydroxide (alum), which is the only adjuvant currently licensed for human use, has a strong T_h2 bias that effectively abrogates CTL responses (4). Subunit vaccines pose no risk of inadvertent infection but tend to have poor immunogenicity without adjuvants. On the other hand, whole-killed vaccines may be virulent with incomplete inactivation or have poor immunogenicity due to the inactivation procedure (e.g., denaturation of epitopes by heat or formaldehyde). In addition, not all pathogens can be grown in tissue culture, making it impossible to produce a whole-killed vaccine from them (3).

Thus, current antigen-based vaccines have several important shortcomings. Although such vaccines have proven highly effective against many diseases, there still remain numerous diseases for which it has not been possible to produce effective and safe vaccines (3, 5). Also, even for diseases for which effective vaccines exist, it may be desirable to develop less expensive, heat-stable, multivalent, single-dose vaccines for use in less-developed countries. DNA vaccines have the potential to overcome many of the limitations of antigen-containing vaccines.

What Are the Advantages of DNA Vaccines?

DNA vaccines, by virtue of the *in vivo* synthesis of antigen, induce both humoral and cell-mediated immunity, and this without the risk of inadvertent infection. Thus, they offer the efficacy of a live, attenuated vaccine with the safety of a subunit vaccine. They also offer, at least in animal models, the possibility of long-lasting immunity without boost (6). This is probably due, at least in part, to the prolonged antigen synthesis. Finally, by virtue of immunostimulatory sequences within their backbone (i.e., CpG motifs, discussed below), they are their own adjuvant and generally induce the highly desirable T_h1-type responses that include CTL and cytokines that can control viral replication.

Other advantages of DNA vaccines may be important for vaccine delivery to less-developed areas of the world. These include the low cost of production, the relative ease of manufacturing (with a single process for all DNA vaccines), and the heat-stability of DNA, obviating the need for a "cold-chain." Also, it should be possible to make multivalent vaccines against several pathogens by cloning genes encoding different antigens into a single vector (for co-linear expression) or by mixing different plasmids together.

How Do DNA- and Protein-Based Vaccines Compare?

Disease-specific, DNA-based immunization has now been demonstrated in animal models against numerous viral, bacterial and parasitic human and veterinary diseases (7, 8). In almost all cases, strong antibody and CTL responses have been noted, and, where it has been possible to test, protection against live pathogen challenge. Our work has concentrated on the development of DNA vaccines against HBV (9), and the remainder of this review will provide an overview of preclinical evaluation of DNA vaccines and protein vaccines with DNA adjuvants for prophylactic or therapeutic immunization against HBV.

The surface coat of HBV is encoded by a single open reading frame divided into three domains (pre-S1, pre-S2 and S) by three separate ATG start codons. As such, three different polypeptides may be made: the small or major surface protein (S), the middle protein (pre-S2 + S) and the large protein (pre-S1 + pre-S2 + S). The HBV envelope contains mostly S protein, with lesser amounts of the larger forms. The B- and T-cell epitopes of the envelope are known collectively as hepatitis B surface antigen (HBsAg) (10).

The current prophylactic vaccine against HBV contains recombinant S protein with alum as adjuvant. When injected into mice, it induces antibodies against HBsAg (anti-HBs) but usually not CTL, owing to the T-helper type 2 (T_h2) bias of the alum. On its own, recombinant HBsAg induces lower levels of anti-HBs and weak CTL (4). In comparison, a DNA vaccine encoding the S gene of HBV, when injected intramuscularly (IM) in mice, induces high titers of anti-HBs and strong CTL responses. Even after a single injection of DNA, high antibody titers are maintained for essentially the life of the mouse (6, 11, 12). HBV DNA vaccines have also been shown to be effective in chimpanzees (13, 14).

In very young mice, protein vaccines are less effective than in adult mice, owing to the immaturity of their immune system. However, DNA vaccines, which can continue to produce antigen until the immune system is mature enough to respond to it, induce strong humoral and cell-mediated responses even in mice as young as one day old. In such young mice, there is no response with a protein-alum vaccine (15).

What Makes DNA Vaccines So Effective?

There are probably three reasons why DNA vaccines are so effective: (i) the *in vivo* synthesis of antigen, which likely occurs in both professional APCs and non-APCs (e.g., skin fibroblasts and muscle cells), leads to appropriate presentation of antigenic peptides in the context of class I and II MHC molecules; (ii) the prolonged synthesis of antigen, which may be "self-boosting"; and (iii) the presence of immunostimulatory CpG motifs in the DNA backbone.

Antigen Presentation

Although direct transfection of APCs is not absolutely essential (16), only professional APCs are able to present the antigen that induces CMI (16–19). Also, it is likely that direct transfection of some APCs (e.g., dendritic cells) does occur. Immediate removal of the target muscle after IM injection of DNA does not diminish CTL responses (20), indicating that plasmid leaves immediately, perhaps via the lymphatic system to regional lymph nodes where it can directly transfect APCs. Removal of the skin target site during the first few days does abrogate the immune response (20), indicating that transfected APCs in the skin do not track immediately to lymphatic tissue. Delivery of DNA vaccines to the skin has been shown to directly transfect APCs (i.e., Langerhans' cells) (21). While APCs are essential for initiating immune responses, it is probable that antigen released from other transfected cells (e.g., muscle) can help boost antibody production by B-cells.

Longevity of Antigen Expression

In theory, antigen expression from plasmid DNA can continue for a long period, and in a post-mitotic cell such as the muscle fiber, indefinitely. However, in fact, antigen-expressing muscle cells are destroyed around 10–20 days after DNA injection by an immune-mediated mechanism, since it does not occur in mice with severe combined immunodeficiency (SCID) (6). It is likely that antigen-specific CTL destroy antigen-expressing cells by virtue of their presentation of antigenic peptides on MHC class I molecules.

Immunostimulatory CpG Motifs

CpG motifs are unmethylated cytosine-guanine dinucleotides commonly found in bacterial but not vertebrate DNA; they cause potent activation of the innate immune system. It appears that the mammalian immune system has evolved the capability to recognize and respond to such CpG motifs as an early immune activation to help fight off bacterial infection. Bacterial DNA or oligonucleotides containing CpG motifs (CpG ODN) cause B-cell proliferation and immunoglobulin secretion, monocyte cytokine secretion, and activation of natural killer (NK) cell lytic activity and increased cytokine secretion (especially T_h1 cytokines such as IFN-γ, TNF-α and IL-12) (22, 23). CpG ODN can also act to augment antigen-specific responses owing to: (i) a synergy of CpG effects on B-cells and B-cell activation through antigen-receptors, (ii) direct effects on APCs (i.e., dendritic cells), such as up-regulation of co-stimulatory molecules, which can improve T-cell activation, and (iii) induction of cytokines that in turn augment both antibody and CTL responses. Since plasmids contain many CpG motifs, DNA vaccines can act as their own adjuvant, and indeed it has been demonstrated that DNA vaccines are dependent on the presence of such motifs to be effective (24–26).

We have also evaluated CpG ODN with recombinant HBsAg in mice and show it to be a potent adjuvant for induction of T_h1-type responses, including CTL and predominantly IgG2a antibodies (4). The T_h1 response dominates over the T_h2 response of alum when the two adjuvants are administered together. Furthermore, CpG ODN can redirect a previously established (with alum) T_h2 response to a T_h1 response, even in very young mice (15).

What Is the Need for a DNA Vaccine Against Hepatitis B?

Hepatitis B poses a serious worldwide problem (27). Most infected adults recover completely, sometimes without even realizing that they were infected, and only a small proportion (< 1%) may die from fulminant hepatitis. A more serious problem is that of chronic infection, with 5–15% of infected adults and 90–95% of infected newborns failing to clear infection. There are an estimated 300 million individuals chronically infected with HBV today; and in addition to serving as reservoirs of HBV, they run a greatly increased risk of developing cirrhosis and hepatocellular carcinoma (10).

There are highly effective prophylactic vaccines available for HBV; however, these usually require three doses over 6 months, and that is unacceptably long for persons at risk of exposure to HBV (e.g., health care professionals). Even after three doses, up to 15% of individuals (depending on age and immune status) do not respond adequately, and in at least some cases, this is genetically determined (28–30). Based on animal studies, DNA vaccines may be able to induce immunity more quickly and in a greater proportion of the population. In particular, DNA vaccines may be more effective for immunization of newborns, especially those born to chronic carrier mothers. Furthermore, the protein vaccine is relatively costly to manufacture, making it prohibitively expensive for delivery to some of the poorer countries. DNA vaccines are inexpensive to manufacture, and delivery to less-developed areas of the world is facilitated by the fact that they are heat stable and do not require refrigeration.

There is currently no effective treatment for chronic HBV infection. Chronic carriers of HBV who eventually overcome infection, either spontaneously or as a result of interferon therapy, acquire a broad range of anti-HBV immune responses similar to those developed by persons recovering from acute infection. These include HBV-specific CTL and T_h1 cytokines, which may be important for non-cytopathic control of viral replication. Successful immunotherapy for chronic HBV infection will likely involve induction of such T_h1-like immune responses. DNA vaccines may be one approach that can induce such immune responses. Of particular interest is the fact that DNA vaccines are especially effective in inducing CTL. Although not essential for protective immunity against HBV, CTL may be important for avoiding or overcoming the chronic carrier state. Indeed, many previously infected individuals, even years after clinical and serological recovery, have traces of HBV in their blood and HBV-specific CTL that express activation markers indicative of recent contact with antigen (31). These results suggest that sterilizing immunity may not occur after HBV infection and that chronic activation of CTL is responsible for keeping the virus under control.

Transgenic mice that constitutively express HBsAg in the liver are a model of the neonatally infected "healthy" chronic HBV carrier, in that they are tolerant to the high levels of circulating antigen and do not produce any anti-HBs antibodies. DNA-based immunization of such HBsAg-transgenic mice by IM injection of HBsAg-expressing DNA results in a rapid appearance of anti-HBs antibodies and a concomitant loss of circulating antigen, which is largely due to down-regulation of transgene expression in the liver (32). This appears to be T-cell dependent (both CD4+ and CD8+) and B-cell independent, based on results after passive transfer of cells from normal mice immunized with HBsAg-expressing DNA. The T-cell effect is predominantly non-cytolytic, since there is no elevation of liver enzymes in the serum, nor is there any histological evidence of liver necrosis at the time that circulating HBsAg is rapidly decreasing. It is probably due to a cytokine-mediated effect, since in a similar transgenic model it was shown that passive transfer of HBsAg-specific CD8+ CTL caused a transient down-regulation of HBV transgene expression which was mediated in a predominantly non-cytolytic fashion by IFN-γ and TNF-α (1, 2, 33, 34).

What Are the Safety and Regulatory Issues?

Several issues are being carefully considered as DNA vaccines go into clinical trials.

Possibility of Tolerance to Foreign Antigen

One of the initial worries was that continuous expression of the antigenic protein (in particular in muscle, which is post-mitotic) might induce immunological tolerance. This was based on the finding that luciferase reporter gene expression could continue for nearly two years in muscles of mice (35). However, luciferase appears to be an exceptional protein that is very poorly immunogenic, at least in mice. After IM injection of plasmid DNA encoding an antigenic protein such as HBsAg, expression continues for only a few weeks, owing to immune-mediated destruction of the antigen-expressing cells (36). In any event, tolerance has never been demonstrated for any of the many animal models of DNA vaccines developed to date.

Possibility of an Integrative Event

Another safety concern is the possibility that the DNA may integrate into the host's chromosomal DNA and cause an insertional mutagenic event by activation of a proto-oncogene or by inactivation of a tumor suppresser gene. The likelihood of an insertional mutagenic event is low, since: (i) most injected DNA is rapidly degraded in the extracellular space; (ii) the plasmid DNA vectors are designed to remain episomal; (iii) most non-integrated DNA would soon be lost during subsequent cell division; and (iv) integration is not possible in mature muscle fibers as they are permanently post-mitotic. The incidence of an insertional mutagenic event is estimated to be 10^3 times lower than the rate of spontaneous mutagenesis (37).

Possibility of Immune Response to DNA and Induction of Autoimmune Disease

Plasmid DNA can induce the production of antibodies against single- but not double-stranded DNA; however, anti-ssDNA antibodies are not pathogenic, and the fear that they could contribute to undesired autoimmune reactions against the host's DNA has not materialized, even in lupus-prone animal models (38–40).

Other Unwanted Immunostimulatory Effects

The adjuvant effect of CpG motifs appears to be a desirable and necessary event for the induction of strong immune responses with DNA vaccines. Nevertheless, there may be situations where a strong T_h1 stimulatory effect that includes IL-12 induction is undesirable, such as in persons prone to autoimmune disease.

How Do DNA Vaccines Work in Humans?

Encouraged by the extremely good responses obtained in animal models, researchers have carried out several clinical trials using DNA vaccines (41 – 44). However, results have been disappointing, indicating the need to further improve DNA vaccines. Increased efficacy could result from improvements in efficiency of transfection, in expression of antigen, or in the induction of immune responses against the antigen.

Efficiency of Transfection

Pure plasmid DNA does not transfect with a high efficiency many cell types other than mature skeletal muscle fibers. The use of delivery systems, especially targeted delivery systems, may help overcome this. In particular, it may be desirable to target DNA vaccines to APCs, since it is now clear that antigen must be presented by professional APCs. However, any delivery system will most likely increase the cost and complexity of vaccine manufacturing.

Increased Expression of Antigen

Changes in vector design may allow increased expression of antigen by having stronger promoters or increased stability of the mRNA through the addition of introns.

Enhanced Immune Responses to Expressed Antigen

Various strategies to enhance immune responses following DNA-based immunization have been reported. These include the addition of CpG immunostimulatory motifs (24 – 26) and the use of other non-DNA adjuvants (45). It is also possible to improve immune responses through the co-expression of cytokines (46, 47) or co-stimulatory molecules (47, 48).

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Current Controversies in Screening:

Cholesterol, Breast Cancer, and Prostate Cancer

Harold C. Sox, M.D.

Abstract

Physicians must make decisions in day-to-day practice even when the balance of benefit and harm is not yet known. Adopting a clinical policy about screening is a case in point. Three controversies in screening healthy adults illustrate different aspects of resolving a dispute when the evidence is incomplete.

The major controversy in cholesterol screening is whether to screen young adults. There has never been a randomized trial of treatment, let alone a trial of screening, in young adults. However, a patchwork of evidence strongly suggests that, because the baseline risk of coronary heart disease (CHD) is very small in young adults, the absolute reduction in risk from treatment would be very small.

In breast cancer screening, randomized trials do not show conclusively that periodic mammography for women aged 40–49 years reduces breast cancer mortality. A 7–10 year delay between the first mammogram and a reduction in deaths from breast cancer suggests the hypothesis that the only benefit of screening women aged 40–49 years occurs from mammograms performed after age 50.

There is no high quality evidence that early detection and treatment reduce the death rate from prostate cancer. In lieu of randomized trial data, we must depend on a decision analysis that shows that screening middle-aged men is cost-effective relative to other preventive services. However, this result depends on using optimistic survival data in the decision model, and most organizations do not recommend routine screening. The best strategy is to discuss the harms and benefits, and let the patient decide. **Key Words:** Screening, breast cancer, prostate cancer, coronary heart disease.

Several contemporary controversies about routine screening illustrate the challenges in developing recommendations for clinical practice when the evidence is of poor quality, incomplete, or conflicting. Controversy develops under these circumstances because physicians differ in how they respond to the need to take a stand in the care of individual patients. Some physicians believe that the best way to serve the patient is to provide a service until it has been discredited, while others believe that the patient is best served by withholding a service until it has been proven effective.

This article updates a 1995 review of preventive services (1). I write as the chair of the second U.S. Preventive Services Task Force, which made its report in December 1995 (2). The Task Force began by selecting target conditions on the basis of their prevalence, severity, and susceptibility to successful treatment. A systematic search of the literature and assessment of study methods identified high-quality studies. The Task Force was at pains to link its recommendations to the evidence in these studies. The final step was extensive external review, in which experts had a chance to persuade the Task Force to adopt their perspective on specific preventive methods. The Task Force graded the strength of its recommendations. Some recommendations had a strong base of evidence for (A or B recommendations) or against (D and E recommendations), but many recommendations received a C rating, which meant that it was not possible to make a firm rec-

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ommendation, either because the studies were of poor quality or because they were of good quality, but with conflicting findings. The rating scale serves partly to spotlight opportunities for research, but mostly to help physicians set priorities for using a limited time in the office. Physicians should spend time on A- and B-rated services and not find themselves doing C-rated items, let alone D- and E-rated services, at the expense of the A- or B-rated services.

Screening is a low-yield activity on a year-to-year basis, yet it will repay persistent effort, since the lifetime incidence of many diseases is quite high (Table 1). The annual incidence of invasive cervical cancer is only 20 women per 100,000, aged 40 years. Yet, in a lifetime, 0.7% of all women will develop cervical cancer. So, physicians should not get discouraged with screening because they can't remember the last time they made a diagnosis of cancer with a screening test.

When to Start Screening for High Serum Cholesterol?

The first topic is when to start screening for high serum cholesterol levels. The resolution of this issue is methodologically challenging. It pits two points of view against one another.

The National Cholesterol Education Project recommends that the screening of men and women begin at age 20 and continue every 5 years thereafter (4). The authors do not explain the logic of screening every 5 years regardless of whether the patient's cholesterol is very close to a treatment threshold, or is 150 mg/dL and would never reach a treatment threshold. The rationale for the recommendation to start at age 20 is that arteriosclerosis is a progressive disease that begins early in life and is linked to an elevated serum cholesterol; so the earlier one begins to reduce any contributing factor, the better. This position is based on physiologic reasoning, not experimental evidence. Lowering serum cholesterol does lower the risk of heart disease in individuals in their 40s, 50s and 60s. Because there have been no studies of the effect of lowering cholesterol in individuals who are in their 20s and 30s, there is no direct evidence that treating young people reduces the incidence of coronary heart disease.

The U.S. Preventive Services Task Force (2) and the American College of Physicians-American Society of Internal Medicine (ACP-ASIM) (5) both recommend that screening begin when the risk of coronary heart disease becomes appreciable. Their logic is the following: Screen only at an age when you are willing to treat. (Some would take issue with this premise, believing that people are more likely to reduce their dietary intake of cholesterol and saturated fat if they know that their serum cholesterol is high. This belief is unsubstantiated by any evidence that knowing one's cholesterol alters behavior). Moreover, treatment of high cholesterol may not be entirely safe. Some treatments for high cholesterol have increased the risk of all-cause mortality in populations at low risk for coronary heart disease. Therefore, in the lifetime of a person with high serum cholesterol, there may be periods in which the risk of coronary disease, and therefore the probability of benefit from treatment, is very low, yet the person may suffer side effects or long-term harms, to which everyone is susceptible. Why treat during a time of life in which harms exceed benefit, as long as there is no penalty for delaying treatment until an age in which benefit exceeds harms? In fact, with treatment, a person's risk of coronary disease falls remarkably quickly to the same level as the risk of someone who had spent a lifetime at the post-treatment cholesterol level. This crucial piece of evidence suggests that it is not necessary to begin treatment very early in life in order to reduce the risk of coronary disease. Therefore, treat when the immediate risk of coronary disease starts to rise and avoid treating at an age when the harm may exceed the benefit. The evidence supporting this line of argument is strong.

As the risk of a disease increases, the benefits of treatment increase relative to the harms. The

TABLE 1

Annual and Lifetime Incidence of Some Common Cancers

	Annual incidence at age 35 – 39 years per 100,000 persons	Annual incidence at age 75 – 79 years per 100,000 persons	Lifetime incidence
Breast cancer	63	327	9.3%
Colon cancer (men)	5.9	411	6.0%

Source: Reference 3. Reprinted with permission of the Annals of Internal Medicine.

best way to understand this principle is to consider a hypothetical circumstance: a fatal disease that, because it cannot be diagnosed in an early, treatable stage, requires prophylactic treatment for everyone (Table 2). The treatment reduces the risk of death by 50% in those who have the disease and increases the risk of death by a tenth of a percent in those who don't have the disease. Treating a population in which there are 20 people per 100,000 with the disease reduces the number of deaths with the disease from 20 to 10 per 100,000. However, this treatment will cause100 deaths per 100,000 (one death per 1,000) in those who don't have the disease. The number of deaths in those fated to die decreases, but the overall number of deaths increases (Table 2). If the risk of death from the disease is much higher (1%), the balance of harms and benefits changes dramatically. Treatment saves 500 of the 1,000 people who had the disease. Although treating those who don't have the disease causes 100 deaths, the overall number of deaths decreases by 400. Clearly, the balance between harm and benefit depends on the baseline risk of the condition to be treated.

The treatment of high cholesterol is an excellent example of the changing balance of benefits and harms, as disease risk increases. In a meta-analysis of a very large number of studies of different drug treatments for high cholesterol, the authors grouped the studies according to the coronary heart disease (CHD) mortality rate in the study population, as indicated by the death rate in the untreated group (6). The high risk population clearly benefited from treatment, with an odds ratio (O.R.) of 0.75 for total mortality. However, in the group with the lowest CHD mortality rate, treatment was associated with an increased total mortality rate (O.R.=1.3). Clearly, the balance of harms and benefits shifted from net benefit to net harm with a falling risk of CHD in the population, a relationship that supports the view that cholesterol-lowering drugs might cause harm in low-risk populations, such as young adults.

However, this meta-analysis included studies of treatments that are no longer used, in part because of adverse effects. Perhaps, modern cholesterol-lowering drugs are so safe that they would not cause net harm in low-risk adults. Clinical trials of several statins have shown a reduction in risk of future CHD events in hypercholesterolemic patients with angina pectoris or myocardial infarction (7), asymptomatic hypercholesterolemic high-risk middle-aged men (8), men and women with a normal cholesterol level who have survived a myocardial infarction (9), and men and women with average cholesterol levels but below-average HDL levels (10). A meta-analysis of 16 clinical trials of statin drugs showed a 22% reduction in total cholesterol, 29% reduction in risk of stroke, 22% reduction in total mortality, and 28% reduction in cardiovascular disease mortality (11). This structured review did not detect an increase in non-cardiovascular disease mortality, including cancer. However, as the authors pointed out, the confidence intervals on the estimated risk were wide, and the average period of follow-up was only 3.3 years. In one study (9), breast cancer occurred in 12 patients in the group taking pravastatin and one patient in the placebo group (p=0.002). These results underscore the need for caution in prescribing statins to patients who are at low risk of heart disease. None of these clinical trials enrolled healthy young men and women, the population in question when considering the age to start screening healthy individuals.

The rationale for screening at an early age hinges on the early onset of atherosclerosis and

TABLE 2

Effect of a Prophylactic Treatment for a Hypothetical Fatal Disease

	Number who have disease		Number who don't have disease		
	die	live	die	live	net deaths
Low-risk population					
Status quo	20	0	0	99,980	
Treat	10	10	100	99,880	+90
High-risk population					
Status quo	1,000	0	0	99,000	
Treat	500	500	100	98,900	−400

Assumptions:

Disease fatal unless treated

Treatment reduces the risk of death by 50% in those with disease

Treatment increases the risk of death by 0.1% in those who don't have disease the purported advantage of intervention at an early stage in the development of atherosclerotic plaque. Without studying the effect of cholesterol lowering in young people, it is very difficult to test this rationale. One approach, however, is to examine the rate at which the incidence of CHD falls after starting cholesterol-lowering drugs and the extent to which it approaches the incidence of CHD in cohort studies of people who had spent their lifetime with a serum cholesterol equal to the post-treatment cholesterol level. Delaying screening and treatment until an age when the CHD incidence started to rise would be safe if the annual incidence of CHD rapidly fell to the lowest level that one could expect, that of individuals who had always been at the post-treatment cholesterol level.

Law and colleagues (12) compared the incidence of CHD before and after treatment achieved a 10% reduction in serum cholesterol with the CHD incidence in cohorts whose lifetime cholesterol levels differed by 10%. The left-hand bar in Fig. 1 represents a 27% difference in CHD incidence between two cohorts of men aged 55–64 who differ by 10% in their serum cholesterol concentration. The 27% difference in CHD incidence is the maximum effect that one could expect from reducing the serum cholesterol concentration by 10%. The middle bar represents the fall in CHD incidence in the first two years (a 7% drop) after achieving a 10% reduction in serum cholesterol concentration. At five years, the fall in CHD incidence is 25% (95% confidence interval, 15–35%), which is not substantially different from the 27% theoretical maximum fall in CHD incidence. So, cholesterol treatment does not require fifteen years to achieve a desirable risk reduction. Five years is enough. Put another way, people don't have to pay a penalty for waiting to lower cholesterol until an age when the incidence rises to the point where the benefits of lowering cholesterol exceed the potential harms.

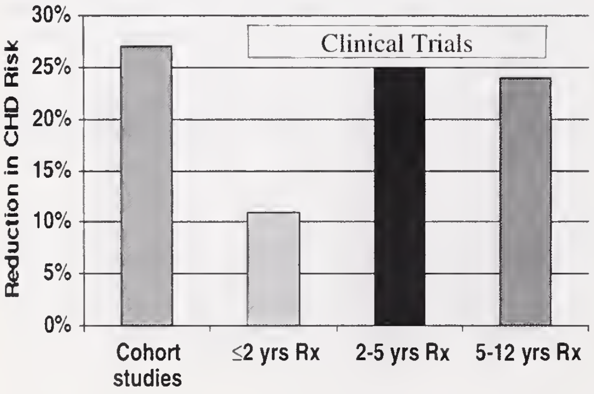

Fig. 1. Effect of a 10% reduction in serum cholesterol on risk of coronary heart disease. The left-hand bar represents the difference in risk for two cohorts of middle-aged men whose cholesterol levels are 10% apart and whose age at death was 55–64 years. The other bars represent the change in coronary heart disease risk seen in randomized trials of cholesterol lowering in the first two years of treatment, between the second and fifth years of treatment, and between the fifth and twelfth years of treatment. Adapted from tables that appeared in Reference 12 and used with permission of the British Medical Journal.

The reduction in the probability of developing CHD (often called absolute risk reduction or attributable risk) is the most useful measure of the effect of lowering cholesterol. The inverse of the reduction in the probability of developing CHD is the number of people who must undergo treatment for one person to avoid developing CHD, which is a crude measure of cost-effectiveness. The reduction in the probability of developing CHD is the reduction in relative risk (e.g., 25% reduction in CHD incidence) multiplied by the pre-treatment incidence of CHD. The relative-risk reduction decreases with age, from 54% at ages 35–44 to 19% at ages 75–84 (12), but the incidence of CHD increases at a much faster rate with advancing age, as shown for men and for women in Fig. 2, so that the absolute risk reduction should increase with age.

In fact, the absolute reduction in risk of CHD does increase dramatically with advancing age (5). Fig. 3 shows the effect of lowering cholesterol from 280–240 mg/dL as a function of age (5). Because the pre-treatment risk of CHD is so low in men and women in their 30s (and would be even lower in the 20s), the absolute risk reduction is very small. On the other hand, the absolute reduction in the risk of CHD becomes larger as the pre-treatment risk increases with advancing age.

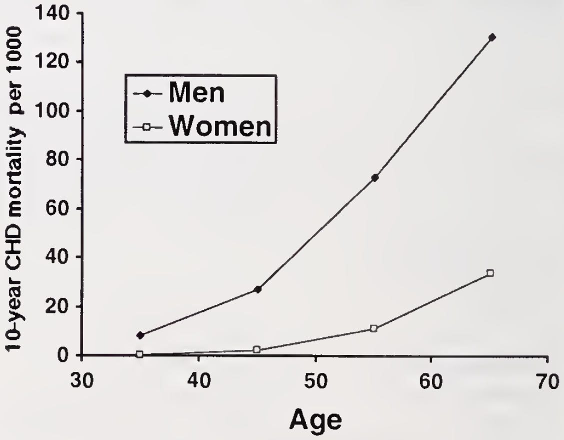

Fig. 2. Age and risk of CHD: the findings represent average risk individuals with serum cholesterol equal to 280 mg/dL. Adapted from a table in Reference 5 with permission of the Annals of Internal Medicine.

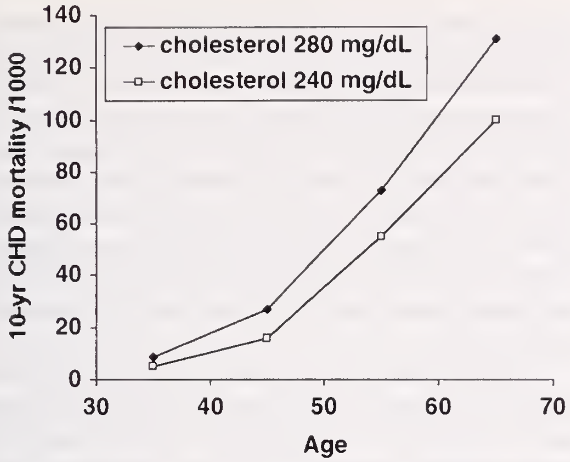

Fig. 3. Effect of lowering cholesterol on risk of coronary heart disease. The data represent the effect of lowering serum cholesterol from 280 mg/dL to 240 mg/dL in men. Adapted from a table in Reference 5 with permission of the Annals of Internal Medicine.

To summarize, physicians should delay cholesterol screening in healthy people until an age when it is reasonable to prescribe cholesterol-lowering medication. Because there is reason to be concerned about possible ill effects of long-term treatment to reduce serum cholesterol, physicians should be sensitive to the balance of harms and benefits, which shift toward benefits as the baseline risk of CHD increases. The expected benefit of cholesterol reduction, an absolute reduction in the incidence of CHD, is very small until age 35 in low-risk men, and age 45 in women. Since treatment achieves the maximum achievable reduction within five years of starting treatment, there is no penalty for delaying treatment until the age at which the benefit begins to increase. Both the U.S. Preventive Services Task Force and the American College of Physicians—American Society of Internal Medicine (ACP-ASIM) recommend starting to perform screening at age 35 in healthy men and age 45 in women.

These recommendations contrast sharply with those for people with risk factors for CHD, or people with established CHD. These individuals have a much higher incidence of subsequent CHD events than do healthy people. The same logic that applies to healthy people (screen when the incidence of CHD is appreciable) applies to people at high risk of CHD, whom physicians should screen for hypercholesterolemia irrespective of the patient's age.

When to Start Screening for Breast Cancer?

Breast cancer is the second leading cause of cancer death in women. The incidence increases with advancing age, but it is appreciable before age 50 (Fig. 4). The age at which to start screening is a matter of great controversy. Fortunately, there have been many large-scale randomized trials which randomly allocated women to regular mammography or to usual care. The endpoint in these studies was death from breast cancer. A meta-analysis of eight randomized trials (and two case-control studies) shows that performing mammography every 1–2 years on women aged 50 and older reduces by 26% the risk of dying of breast cancer (95% confidence interval, 17%–34%) (13). The same meta-analysis (applied to eight randomized trials and one case-control study) showed different results in women aged 40–49 years. Only five of the nine studies reported a relative risk of dying of breast cancer less than 1.0, although the relative risk was not statistically significantly different from 1.0 in any study. The combined relative risk was 0.93 (95% confidence interval, 0.75–1.13). The apparent difference in breast cancer screening effectiveness in younger women has caused a great deal of discussion about whether the difference is real and, if so, about the reasons for the difference.

An apparent delay in benefit from screening is the most remarkable aspect of screening women who are aged 40–49 at the time of the first mammogram. In women aged 50–69, the relative risk is 0.73 for those who have been followed for 7–9 years, and 0.76 for those who have been followed for 10–12 years (13). In women aged 40–49, the relative risk is 1.02 (95% confidence interval, 0.82–1.27) for those who have been followed for 7–9 years and 0.83

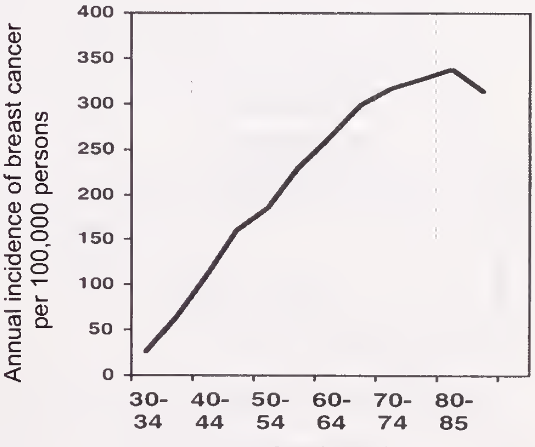

Fig. 4. Incidence of breast cancer according to age. Data obtained from a table in *Common Screening Tests* (Reference 3) and used with permission of the American College of Physicians.

(95% confidence interval, 0.65 1.06) for those who have been followed for 10–12 years (13). The difference between younger and older women is even clearer in the curves describing breast cancer deaths in the first 12 years after screening, in a meta-analysis of five Swedish randomized trials (14). In women aged 50–69, the curves describing mortality in the screened group and the control group separate at about 4 years and diverge progressively with each year of follow-up. In women aged 40–49, the curves are essentially superimposable for the first 11 years, diverging thereafter. Fig. 5 illustrates this effect.

Why does it take at least several years for the survival curve for screened women to diverge from the curve for unscreened women? Regardless of the age of the patient, the survival curve for screened women should be very close to the curve for unscreened women for the first few years after the first mammogram. Immediately prior to the first mammogram, a cohort of screened women should have the same proportion of metastatic cancers as a cohort of unscreened women. Consequently, screened and unscreened women should have the same death rate for the first few years, as deaths from these metastatic cancers occur. However, the first mammogram detected cancers that were successfully treated in screened women but would go on to metastasize in unscreened women. If the second mammogram is close enough to the first mammogram, fewer of the cancers it detects will have metastasized, relative to the cancers in the cohort of unscreened women. Therefore, the survival curves should begin to diverge.

Given this rationale, why does it take so much longer for the survival curves to diverge in women aged 40–49 years (15)? One hypothesis is that breast cancer metastasizes earlier in younger women, so that the interval between mammograms is too long to detect many cancers before they metastasize. Breast cancer does grow more rapidly in younger women (16). In addition, breast cancer is more likely to have metastasized in younger women: at diagnosis, 44% of women under age 50 years have metastases, as compared with 36% of women aged 50 years and older (17).

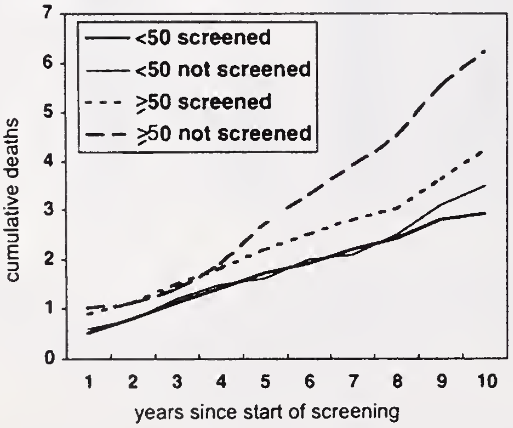

Fig. 5. Cumulative deaths after starting screening in two cohorts. The graphical representation is not based on actual data obtained from Reference 14, but illustrates the differences in the various cohorts which have been studied.

Is the benefit of screening women in their 40s due entirely to improved survival from breast cancer detected in their 50s? This hypothesis receives some support from the HIP study (18). The authors divided women who were 45–49 years old at their first screen into two groups. One group had a diagnosis of breast cancer at age 45–49; the other had breast cancer diagnosed at age 50–54 years. Only the group whose diagnosis of breast cancer occurred at ages 50–54 had better survival than unscreened women. The HIP study findings suggest that the effectiveness of screening in women who are over age 50 may explain effectiveness in women who are age 40–49 at the time they began screening. The number of patients in the HIP study was too small to draw a strong conclusion, but the authors are the only ones to analyze their findings according to the age at diagnosis. Age may simply be an imprecise marker for menopausal status, which is physiologically important in tumor growth. Many women who began these studies before their menopause were probably menopausal at the time of detection of cancer. In some randomized trials, screening did not begin until age 45.

Reasons for the effectiveness of mammography in women over age 50 years include better accuracy and the slower growth rate of cancer in post-menopausal women. The breasts of post-menopausal women have a higher fat content relative to the breasts of pre-menopausal women. The contrast between a breast mass, which has the radiodensity of water, and the surrounding tissue is better if the surrounding tissue is fat, which has a lower radiodensity than water. In fact, the frequency of a positive mammogram in women with breast cancer is 0.87 in women aged 40–49 and 0.94 in women aged 50–59 (19).

The magnitude of harm in mammography is relatively small, but women aged 40–49 need to know about these harms before agreeing to screening, especially since the evidence of benefit is weak in this age group. Compared with women over age 50, women younger than age 50 require approximately 2.5 times as many biopsies and 3 times as many tests to diagnose one cancer (20). False-positive mammograms are very common; in one study, 56% of women aged 40–49 experienced at least one false-positive mammogram, as compared with 47% of women aged 50–74 (21). Anxiety after screening is one reason for concern about a false-positive result. In one study 26% of women who had a false-positive mammogram remained worried, as compared with 9% of women with a normal mammogram (22).

The U.S. Preventive Services Task Force gave an "A" recommendation for breast cancer screening between ages 50–69. The recommendation for women aged 40–49 was a "C" (no compelling evidence for or against screening) (2). In 1997, the National Institutes of Health Consensus Development Conference (23) concluded that "the data currently available do not warrant a universal recommendation for mammography for all women in the forties." Further, they recommended, "Each woman should decide for herself whether to undergo mammography." This advice reflects the panel's feeling that the decision in 40–49-year-old women is a toss-up, a decision between actions that, repeated over many patients, have essentially the same outcome.

Screening for Prostate Cancer

Unlike the situation with breast cancer, there are no randomized trials for prostate cancer screening, nor any useful trials of treatment of early-stage prostate cancer. To evaluate prostate cancer screening, we will use a heuristic called the "chain of evidence." The first link in the chain of evidence is a reasonably priced, safe test that can detect prostate cancer before symptoms occur. The second link is evidence that the prognosis is better in screen-detected cancer. The third link is evidence that screening leads to better outcomes in clinical practice. A strong recommendation for prostate cancer screening would require that each of these links be intact. The next three sections examine the evidence for each of these three links in the chain of evidence.

Prevalence and Detection of Prostate Cancer

Prostate cancer is a common disease, which makes it a potentially attractive target for screening. Autopsies on men who did not have clinical evidence of prostate cancer provide the best information on the prevalence of prostate cancer in candidates for screening. The prevalence of intracapsular prostate cancer that is large enough to cause significant future problems (a tumor volume of 0.5 mL or greater) is 3.5% in men aged 40–49 and increases with age (Table 3) (24). The prevalences in Table 3 are the best approximations of the pretest probability of prostate cancer at the time of screening. How much does the probability change after a rectal examination or a serum prostate-specific antigen (PSA)? Table 4 shows the likelihood ratios for the rectal examination and the serum PSA (24). A suspicious rectal examination increases the odds of intracapsular prostate cancer by a factor of 1.5–2.0, according to the odds ratio form of Bayes' theorem, which states that the post-test odds equal the pre-test odds times the likelihood ratio. A non-suspicious rectal examination decreases the odds of cancer to 0.9 of the starting odds; effectively, a non-suspicious examination has no effect on the probability of cancer. A single measurement of the serum PSA is only slightly better than the rectal examination in predicting localized prostate cancer (Table 4). Still, because the prevalence of prostate cancer is relatively high (pre-test odds of 6:100 in men aged 60–69), the post-test odds are 18:100, corresponding to a probability of 15%. If everyone who had a serum PSA in the range of 4–10 ng/mL had a prostate biopsy, it would require between 6 and 7 prostate biopsies to detect one clinically significant, localized cancer. This price might be reasonable if people with localized cancer could be sure that treatment had a high probability of prolonging their period of healthy life. In fact, there is considerable doubt about the effect of early detection on prognosis in prostate cancer, mainly because the prognosis is good, at least relative to other cancers, in most men with prostate cancer.

TABLE 3

Prevalence of Prostate Cancer in Autopsies of Men Dying Without Known Prostate Cancer

Age (years)	Prevalence of prostate cancer tumor size (Vol. <0.5 mL)	tumor size (Vol. >0.5 mL)
40–49	0.072	0.035
50–59	0.090	0.044
60–69	0.132	0.064
70–79	0.234	0.114
>80	0.258	0.126

Source: Reference 24. Reprinted with permission of the Annals of Internal Medicine.

TABLE 4
Performance of Screening Tests for Prostate Cancer

	Likelihood ratio intracapsular tumor (>0.5 mL)	extracapsular tumor (>0.5 mL)
Serum PSA		
<4.0 ng/mL	0.8	0.5
4.0 – 10.0 ng/mL	2.8	3.2
>10.0 ng/mL	3.0	23.7
Rectal Examination		
Suspicious (Study A)	1.5	8.6
Suspicious (Study B)	2.0	2.7
Non-suspicious (Study A)	0.96	0.53
Non-suspicious (Study B)	0.83	0.73

Source: Reference 24. Reprinted with permission of the Annals of Internal Medicine.

The Natural History of Localized Prostate Cancer

"Does treatment in the early stage of disease improve the prognosis of prostate cancer?" That question, surprisingly, does not have an answer. An expert panel of the American Urological Association analyzed the literature on the outcomes of radical prostatectomy and radiation therapy. The panel (25) stated its main conclusion as follows: "The panel found the outcomes data inadequate for valid comparison of treatments." In other words, deficiencies in the design of published studies made it impossible to decide if treatment prolongs life. Given this shortcoming, another approach to analyzing the effectiveness of treatment is to ask how good treatment would have to be to improve on the natural history of early stage prostate cancer.

The best study of the natural history of early stage prostate cancer is a 15-year study of a prospectively collected cohort of Swedish men with clinically localized prostate cancer (26). None of the men in the final cohort received curative treatment for prostate cancer. The original cohort comprised 642 men with consecutively diagnosed prostate cancer of any stage. The median age of the cohort was 72 years. Three hundred men had localized disease, and 223 elected no curative treatment. Survival was the same in the men who elected no treatment and those who did undergo treatment with curative intent. Among all untreated men with clinically localized cancer, the 15-year survival was 81% (95% confidence interval, 72%–89%). The authors pointed out that this excellent survival left little room for improvement by radical treatment.

There are several important caveats in interpreting this careful study. First, the men were relatively old. Older men are more likely to die of other diseases, and the findings of this study may therefore underestimate the effect of prostate cancer on the death rate. Second, the clinical examination, rather than serum PSA, was the basis for diagnosis. In the Swedish cohort, nearly 50% of those with localized disease had highly differentiated tumors, and only 4.0% had highly undifferentiated tumors. In a population of patients who underwent prostate biopsy after having a serum PSA of 2.4 – 4.0 ng/mL, 80% had tumors that were intermediate in histological differentiation (27). Apparently, a population discovered by PSA testing has less well-differentiated cancers than men discovered by clinical examination. The mean age of the patients detected by PSA screening was 65 years, somewhat lower than the Swedish cohort.

The histologic grade of the tumor has an important effect on mortality. In the Swedish cohort, the 15-year rate of death caused by prostate cancer was 6% for highly differentiated tumors, 17% for moderately differentiated tumors, and 56% for poorly differentiated tumors (26). In a group of patients who met criteria for radical prostatectomy (age < 70 years at diagnosis, clinically localized to the prostate, and highly or moderately differentiated tumors), 15% died of prostate cancer.

To summarize, the natural history of clinically localized prostate cancer is unusually favorable as compared with many other common cancers. In addition to low mortality, disease progression was the exception: only 33% of the Swedish cohort had local progression and 13% had distant metastases after 15 years. This favorable natural history leaves little room for improvement by radical treatment strategies.

Effect of Treatment

There has been only one randomized clinical trial that compared treatment with no treatment (28). This study enrolled 111 men with localized cancer and randomly assigned them to radical surgery or watchful waiting. At 15 years, 21% of the controls and 26% of the radical surgery patients were still alive, and the two survival curves were identical. There was, therefore, no hint of a treatment effect. Because of the small number of patients, there was a large chance of missing a clinically important difference in survival rates. As discussed earlier, the American Urological Association expert panel reported that it was not possible to conclude that radical treatment reduced the prostate cancer death rate (25). Fortunately, several clinical trials are randomly assigning patients with localized prostate cancer to radical treatment or watchful waiting. However, these studies will require at least 10 years to accumulate enough study endpoints to form any conclusions.

What should one do while waiting for the results of randomized trials? Decision analysis offers a method for predicting the results of a randomized trial, based on guesses about the effectiveness of treatment and what is known about the natural history of prostate cancer. There have been several decision analyses of prostate cancer and treatment. The analysis that forms the basis of the practice guidelines of the ACP-ASIM is illustrative of the approach and results (29). These authors performed a cost-effectiveness analysis, which is a method for estimating the costs of screening (as compared with no screening) per added year of healthy life gained by screening. The authors of the decision model used existing knowledge of the prevalence of prostate cancer and the accuracy of tests (Tables 3 and 4), the death rate from surgery, long-term survival with no treatment, the side effects of treatment, and the costs of diagnosis, treatment, and management of metastatic prostate cancer. The data that they used included the following: 56% and 33% of men with localized disease had well-differentiated and moderately differentiated tumors, respectively; 0.5% surgical mortality rate; long-term incontinence, 23%; long-term erectile dysfunction, 61%. They tested several assumptions about the cure rate from radical prostatectomy, 50%, 75% and 100%. They also assigned values between zero and 1.0 to a year of life with incontinence and with erectile dysfunction (quality-adjustment). The main results from this study appear in Table 5.

Overall, the authors found that screening offered potential benefit to men aged 50–69. The cost-effectiveness of screening in this age range was comparable to many other commonly employed screening and treatment practices, even when they made the realistic assumption that the cure rate is only 75%. For men over age 70, the gain from screening was much smaller, and the cost-effectiveness of screening was well outside the range of other widely used medical interventions. The authors generally made assumptions that were favorable to screening. When they substituted cancer-specific mortality rates from studies other than the one they used, the cost per extra year of life increased by a factor of three to four.

TABLE 5
Marginal Cost-Effectiveness Analysis of Prostate Cancer Screening

Outcome measure	Age 50–59	Age 60–69	Age 70–79
Days gained per person screened (discounted)	11	7	3
Years gained per person treated for prostate cancer	3.2	1.6	0.49
Dollars per quality-adjusted life-year gained (assumes 100% cure rate)	$16,029	$27,507	$162,095
Dollars per quality-adjusted life-year gained (assumes 75% cure rate)	$24,868	$46,976	$612,095

Source: Reference 29. Reprinted with permission of the Annals of Internal Medicine.

The cost-effectiveness analysis provides a best estimate of benefit from prostate cancer screening. These benefits are speculative, albeit well grounded, until ongoing clinical trials report their results. In contrast, the harms of prostate cancer screening are not speculative. Radical prostatectomy is a well-established procedure. A telephone survey of Medicare patients who underwent radical prostatectomy (1988–1990) provides the best estimate of the harms of radical prostatectomy as performed in community practice (30). Forty-seven percent (47%) of the men had some incontinence every day; 23% lost more than a few drops of urine, 32% used pads or a penile clamp, and 2% needed an indwelling catheter. Before surgery, 91% of the men had erections sufficient for intercourse. After surgery, 61% had never had an erection; in the month before the interview, only 11% had erections that were firm enough for sexual intercourse. The authors also asked about follow-up treatments for prostate cancer. Thirteen percent had radiation therapy at least one year after surgery. (The presumed purpose of radiation therapy so long after surgery would be to control metastatic disease.) By that time, 10% had anti-androgen therapy, 15% had orchiectomy, and 28% had at least one of the three treatments. Thus, in the community setting, the cure rate of radical prostatectomy is no better than 72%.

The U.S. Preventive Services Task Force gave prostate cancer screening a "D" recommendation, which means "fair evidence against" routine screening (2). The recommendation of the ACP-ASIM (31) reflected the cost-effectiveness analysis shown in Table 5, which suggested that screening could be useful and cost-effective in men aged 50–69 years. The ACP-ASIM recommended against routine screening, proposing that physicians should describe the potential benefits and known harms of screening, diagnosis and treatment, listen to the patient's concerns, and then individualize the decision to screen. In other words, the ACP-ASIM recommended informed consent before screening.

Will educating patients about the harms and potential benefits of prostate cancer screening have any effect? A randomized trial of patient education addressed this question (32). The study subjects were patients attending a scheduled general internal medicine clinic appointment. Based on random assignment, they saw either a videotape about prostate cancer screening or no video. Among the study endpoints was the answer to the following question: "What treatment would you prefer if you had prostate cancer?" Patients who didn't see the video were about evenly split between watchful waiting (39.5%) and radical prostatectomy (41%). Most patients (86%) who saw the video preferred watchful waiting ($p<0.0001$). In follow-up studies, 12% of the video group had a PSA done at the next opportunity, as compared with 23% of the control group ($p=0.041$). The results were similar but the differences were smaller in a study of men attending a free prostate cancer screening clinic.

Questions and Answers

Audience: Will knowing the cholesterol increase the likelihood that the patient will comply with sensible recommendations about diet?

Dr. Sox: We don't know. There has been one study, and I believe that it did not show any effect of knowing one's cholesterol on compliance with diet, or the degree of which the cholesterol was lowered. So, we don't have the evidence right now to argue that you ought to know your cholesterol as a motivator to follow the sensible diet that most physicians recommend to all of their patients. Diet is of limited efficacy. A Step 1 diet only reduces the cholesterol by about 2% in free living subjects. Even a Step 2 diet only reduced cholesterol by about 6% in a study where the authors made extensive efforts to assure compliance.

Audience: Should we be recommending radiation therapy rather than surgery for cancer of the prostate?

Dr. Sox: We don't know whether radiation therapy is as effective as radical prostatectomy for the same reasons that the American Urological Association said that extant clinical trials of radical prostatectomy had too many design flaws to allow any interpretation of the results.

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Complementary Therapies and Traditional Judaism

Fred Rosner, M.D.

Abstract

In Jewish tradition, physicians are obligated to heal the sick and patients are obligated to seek healing from physicians. Judaism also sanctions certain complementary therapies such as prayers, faith healing, and amulets, when used as supplements to traditional medical therapy. Confidence in the healing powers of God through prayer and contrition is encouraged, provided that the patient uses prayer alongside traditional scientific medicine, not as a substitute for it. **Key Words:** Prayers, faith healing, amulets, nostrums, quackery.

Introduction

In Jewish tradition, a physician is given specific divine license to practice medicine. According to Moses Maimonides (1138–1204) and other codifiers of Jewish law, the physician is obligated to use his medical skills to heal the sick. Not only is the physician permitted and even obligated to minister to the sick, but the patients are also obligated to care for their health and life. Men and women do not have title over their lives or bodies, since they are charged with preserving, dignifying and hallowing these. They must eat and drink for sustenance and must seek healing when ill. Thus, the physician has an obligation and authority to heal, and the patient has a co-responsibility to maintain health.

Another cardinal principle in Judaism is that human life is of supreme value. In order to preserve a human life, even observation of the Sabbath and the Day of Atonement may be suspended, as well as all other rules and laws except the biblical prohibitions against idolatry, murder and forbidden sexual relations. Since every moment of human life is of infinite value, one is prohibited from doing anything that might shorten a life, even for only a very short time. Nor may a person turn to treatments known to be ineffective, since this would, by inference, be shortening life. Traditional Judaism does not distinguish between extending a healthy life and extending the morbid phase of life (by artificial means).

How does traditional Judaism view the use of complementary or alternative therapies? It may be somewhat awkward to speak of alternative or complementary therapies in the traditional world of the Bible and the Talmud. Today we refer to practices as "alternative therapies" when they are used instead of, or in conjunction with the accepted normative practice of medicine, which is codified in the world's knowledge base of medical science defined by the canon of instruction in accredited medical schools. Although the concepts of "science" or "scientific" as we know them today first emerged in the nineteenth century, Moses Maimonides, seven hundred years earlier, clearly distinguished between "therapies which heal by nature and whose efficacy is proven by clinical trials" and "therapies of unproven efficacy" (M. Maimonides' Mishnah Commentary on Tractate *Yoma* 8:6).

In talmudic times (2nd–6th centuries, CE), healing arts were taught primarily through

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apprenticeships and from medical books, some of which were written by famous Greek and Persian physicians. None of these precluded a search for other healing modalities. Although the term "complementary or alternative therapy" has a decidedly modern ring to it, a rich biblical, talmudic and post-talmudic literature exists about prayers, amulets, incantations, astrology and nostrums for the healing and prevention of certain illnesses. Does Judaism condone their use, either as a supplement to or as a substitute for conventional medicine? This essay examines this question and concludes that some forms of what we consider "unorthodox therapies" are acceptable in Judaism, whereas others, such as quackery, superstition, sorcery and witchcraft are not. The criterion for rejection is the theological test of God as the Ultimate Healer. Those therapies that rely on God's healing power are acceptable in traditional Judaism, even if they are considered complementary today.

Prayer

At one time or another, most human beings offer prayers for the relief of their own illness or that of others. These prayers may differ in content and in the manner in which they are offered, by both religious and non-religious people (1). Recourse to prayer in Judaism during illness is not necessarily an indication that the person lacks confidence in traditional medical therapy.

The patriarch Abraham prayed for the recovery of Abimelech (Genesis 20:17), and God healed him. David prayed for the recovery of his son (II Samuel 12:16), but his son died. Elisha prayed for the recovery of the Shunamite woman's son (II Kings 4:33), and the boy recovered. King Hezekiah prayed for his own recovery (II Chronicles 32:24), and God added 15 years to his life. The shortest healing prayer on record is the famous one uttered by Moses for the recovery of his sister Miriam, who was afflicted with leprosy. Said Moses: *El na r'fa na la* [O God, heal her, I beseech thee] (Numbers 12:13), and she recovered. These incidents are anecdotal and hence do not constitute scientific, statistical evidence for the efficacy of prayer, but they are certainly worthy of mention.

One should never be discouraged from praying, even under the most difficult and troublesome conditions. The Talmud says (2) that "even if a sharp sword rests upon a man's neck, he should not desist from prayer." On the other hand, a person should never stand in a place of danger and say that a miracle will be wrought for him. One should not count on being cured by direct intervention by God without first having sought out the advice and treatment offered by conventional human medical practitioners. The Jewish attitude toward prayer is succinctly summarized by Jakobovits (3) as follows:

> ...while every encouragement was given for the sick to exploit their adversity for moral and religious ends and to strengthen their faith in recovery by prayer, confidence in the healing powers of God was never allowed to usurp the essential functions of the physician and of medical science.

Amulets

Since antiquity, people have attempted to ward off misfortune, sickness, and "evil spirits" by wearing pieces of paper, parchment, or metal discs inscribed with various formulae which would protect or heal the bearers. Such artifacts, known as amulets or talismans, are frequently mentioned in talmudic literature, where they are called *kemiya*. Consisting either of a written parchment or of roots or herbs, the amulet is worn on a small chain, in a signet ring or in a tube. It was considered to be of proven efficacy when a physician certified that it had cured either one sick person on three different occasions or three different patients. In the ancient world, amulets were considered part of the legitimate therapeutic armamentarium of the physician (4).

According to most rabbinic authorities, there is little or no objection in Jewish religious law to the use of amulets for healing purposes. The rabbinic literature of the past several hundred years is replete with references to amulets as preventives to ward off the "evil eye," to avert demons, to prevent abortion, and to cure a variety of diseases such as epilepsy, lunacy, fever, poisoning, hysteria, jaundice, and colic (5). Even Maimonides, who seriously questioned the efficacy of amulets, allowed them to be worn and/or carried, even on the Sabbath, because of their possible psychological and placebo effects on the patient's illness (Code of Maimonides, Laws of the Sabbath 19:13-14). The use of amulets is quite widespread even today, particularly among Jews of Moroccan origin living in Israel, and other Sephardic Jews.

Astrology

The generally prevalent belief in astrology in ancient and medieval times was fully shared by the Jews, many of whom believed that the celestial bodies had the power to influence human destiny. Astrologers ascribed occult virtues of heavenly bodies to earthly objects. Treatment for various illnesses consisted of a special image made by an artist, with due reference to the appropriate constellation. For example, Rabbi Solomon ben Abraham Adret, known as *Rashba*, writes that people used to engrave the image of a tongueless lion on a plate of silver or gold to cure pains in the loins or in the kidneys (Response *Rashba* 1:167).

Moses Maimonides was one of the few authorities who not only dared raise his voice against this almost universally held belief, but even branded it as a superstition akin to idolatry. He unequivocally prohibited anyone from being influenced by astrology, and claimed that such practice was an offense punishable by flogging. He categorically rejected astrology (and other superstitious practices and beliefs), and denounced it as a fallacy and delusion (6), an absurd idea (7), and an irrational illusion of fools who mistake vanity for wisdom, and superstition for knowledge (8). Many talmudic and post talmudic rabbis believed in astrology; a few, such as Maimonides, did not. Traces of the belief are found in words and phrases such as *mazal tov* (meaning a good star or planet), still used by Jews today.

Medical Charms and Incantations

An incantation is a recitation over a patient, designed to neutralize harm or illness, and intended to induce healing. The medical effectiveness of incantations in classic Jewish sources was never in doubt. Incantations to heal a scorpion's bite are permitted even on the Sabbath, as is charming a snake or scorpion to prevent injury or harm. The Codes of Jewish Law of Maimonides and of Joseph Karo (1488 – 1575) point out that such incantations are absolutely useless, but are permitted because of the patient's dangerous condition, so that he should not become distraught. The main question concerning the permissibility of incantations in Judaism is whether or not they represent a form of forbidden heathen practice, since Jews are commanded not to go in the ways of the Amorites (Leviticus 18:3). Some talmudic sages declared that if one whispers a spell over a bodily illness, one is deprived of everlasting bliss, i.e., the world to come. On the other hand, the Talmud clearly states that whatever is used for healing purposes is not forbidden.

Zimmels (9) lists a variety of diseases supposedly cured by medical charms and incantations, including certain eye diseases, headache, infertility and epilepsy. .

Nostrums

Zimmels (9) also describes the custom of transference, whereby an illness can be transferred to an animal or a plant by a certain procedure with or without the recitation of an incantation. For example, patients with jaundice were told to put live fish under their soles to transfer the jaundice to the fish. In more recent times, pigeons have been placed on the abdomen of jaundiced patients to transfer the illness to the pigeons and facilitate recovery of the patient (10). This type of remedy is called a *segulah* or nostrum, a form of medical treatment that has no rational or scientific basis other than as a placebo. Nonetheless, the efficacy of this unorthodox therapy is not in doubt to those who recommend it. A *segulah* is an alternative or unconventional or unproven medical therapy having a place in traditional Jewish practice alongside traditional scientific medicine. The current popular belief among some Jews of the therapeutic efficacy of pigeons in the treatment of jaundice is based on the concept of organic disease transference from the patient to a non-human living animal; it has its parallel in the transference of sins from humans to animals in certain religious rituals.

The subjects of charms, incantations, nostrums, magic and other similar topics are complicated. There are rabbis who believe in them, those who oppose them, and those who say they do no harm. The interested reader is referred elsewhere for more details (11 – 12).

Quacks and Quackery

Jewish law requires a physician to be skilled, well educated and ethical. And Judaism has always held the physician in high esteem. Ancient and medieval Jewish writings contain many expressions of admiration and praise for the "faithful physician." In contrast, quacks are those who lie and deceive by pretending to have knowledge and skills that they lack.

Therefore, it is not surprising that the derogatory talmudic statement "the best of healers is destined for Gehinnom" (Tractate *Kiddushin,* Chapter 4:14) generated extensive discussion and commentary throughout the centuries (13). (Gehinnom is the name of the locale reserved for the wicked after death.) Jakobovits states that this phrase was never intended as a denunciation of the conscientious practitioner, but rather is addressed to quacks who claim to be "the best of healers."

Physicians are among a group of communal servants who have heavy public responsibilities and are warned against the danger of negligence or error. The talmudic epigram with its curse is limited to physicians who are overly confident in their craft, who are guilty of commercializing their profession, who lie and deceive as do quacks, who fail to acknowledge God as the true Healer of the sick, who fail to consult with colleagues or medical texts when appropriate, who perform surgery without heeding proper advice from diagnosticians, who fail to heal the poor and thus indirectly cause their death, who fail to try hard enough to heal their patients, or who otherwise fail to conduct themselves in an ethical and professional manner (14).

Summary and Conclusion

Judaism considers a human life to have infinite value. Therefore, physicians and other healthcare givers are obligated to heal the sick and prolong life. Physicians are not only given divine license to practice medicine, but are also mandated to use their skills to heal the sick. Failure or refusal to do so with resultant negative impact on the patients constitutes a transgression on the part of the physician. Physicians must be well trained in traditional medicine and licensed by the authorities.

Patients are duty bound to seek healing from a physician when they are ill; they must not rely solely on divine intervention or faith healing. Patients are charged with preserving their health and restoring it when ailing in order to be able to serve the Lord in a state of good health. Quackery is not condoned in Judaism, even when it is practiced by physicians.

On the other hand, Judaism seems to sanction certain complementary or alternative therapies such as prayers, faith healing, amulets, incantations and the like, when used as a supplement to traditional medical therapy. However, the substitution of prayer for rational healing is condemned. Quackery, superstition, sorcery and witchcraft are abhorrent practices in Judaism. However, confidence in the healing powers of God through prayer and contrition is encouraged and has a place alongside traditional scientific medicine (15).

Epilogue

Alternative or complementary medicine continues to be hotly debated in the scientific community (16). Many practitioners of herbal and other alternative therapies are physicians. Others argue that alternative therapies must never displace or replace proven conventional treatment (17). This essay presents a religious perspective based on ancient and medieval Hebrew writings on this modern debate.

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Colonic Obstruction Due to Sigmoid Muscular Hyperplasia

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AND JACK FARMAN M.B., CH.B.[4]

Abstract

We report a case of acute colonic obstruction initially presumed to be secondary to acute diverticulitis, necessitating emergent surgical intervention. Pathologic examination failed to reveal evidence of inflammation, fibrosis or neoplasia. Marked hypertrophy of the sigmoid circular muscle layer was documented and thought to be the etiology of the colonic obstruction. **Key Words:** Colon obstruction, sigmoid colon, muscle hypertrophy, barium enema.

DIVERTICULAR DISEASE IS ENDEMIC in the Western world, affecting approximately one third of the population over the age of sixty years (1). Most often, diverticula remain clinically silent. Diverticular disease becomes clinically evident as lower gastrointestinal bleeding or lower abdominal pain, which may be complicated by perforation and abscess formation. When lower abdominal pain becomes manifest, there is a tendency to attribute this symptom to superimposed inflammation or diverticulitis. In 1963, Morson (2) showed that fully one third of the specimens resected with a clinical and radiological diagnosis of diverticular disease failed to show any evidence of inflammation. Diverticular disease is primarily a condition of disordered muscle function, the clinical importance of which is often underestimated. In fact, until the mid-1970s, surgical sigmoid myotomy was not uncommonly performed in patients with complicated and uncomplicated diverticular disease, with varied results (3, 4).

Not uncommonly, acute inflammation of the sigmoid colon manifests itself with colonic obstruction; it is usually partial in nature and related to the accompanying inflammation and edema. Complete bowel obstruction due to diverticular disease, on the other hand, is rare. Where complete obstruction occurs in diverticular disease, it is most frequently the result of complicating perforation, infection with abscess formation, edema and spasm (5). We present a rare case of complete colonic obstruction secondary to sigmoid muscular hyperplasia in the absence of inflammatory changes—a condition which necessitated emergent surgical intervention.

Case Report

A 76-year-old man with a history of schizophrenia was admitted to the hospital for treatment of pneumonia. At the time of admission, he was noted to have mild abdominal distension. A reliable bowel habit history could not be obtained from him. With the institution of intravenous antibiotics, his pneumonia resolved. However, his abdominal distension progressed over the ensuing five days, with development of obstipation. Acute bowel obstruction was suspected.

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Radiographic examination of the abdomen revealed an enormously distended colon extending to the left iliac fossa in the erect position. No small bowel dilation was noted. A barium enema confirmed an obstruction in the sigmoid colon. Scattered diverticula were identified in the region of the obstruction (Fig. 1). No extravasation of contrast material was seen. The impression was that of acute colonic obstruction secondary to diverticulitis. It was felt that an underlying colonic neoplasm could not be excluded with certainty.

At laparotomy, a firm mass was palpated in the sigmoid colon. To decompress the massively distended bowel, a diverting transverse colostomy was performed. A follow-up barium enema via both the rectum and transverse colostomy again demonstrated the obstructed sigmoid colon. The unfilled segment of colon measured 8.0 cm in length. Following sigmoid resection, the patient made an uneventful recovery.

Pathological examination of the specimen revealed marked stenosis of the sigmoid lumen (1.2 cm in diameter) and a grossly thickened bowel wall (1.7 cm in width). The stenosed segment (arrow) contained three large diverticula (Fig. 2). The colon proximal to the stenosed segment was greatly dilated, measuring 13.0 cm in circumference and 0.5 cm in thickness.

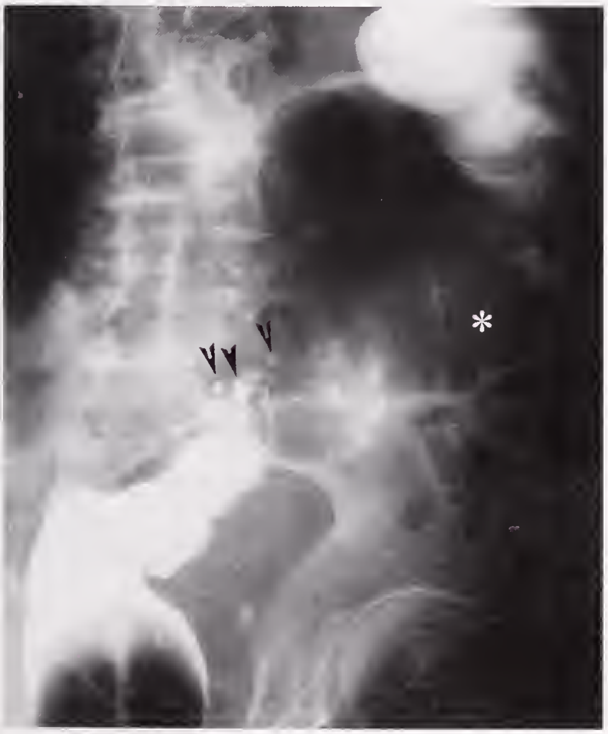

Fig. 1. Obstruction to the retrograde flow of barium in the sigmoid colon. Several scattered diverticula (arrowheads) can be seen. The adjacent descending colon (*) is markedly distended with a small amount of barium.

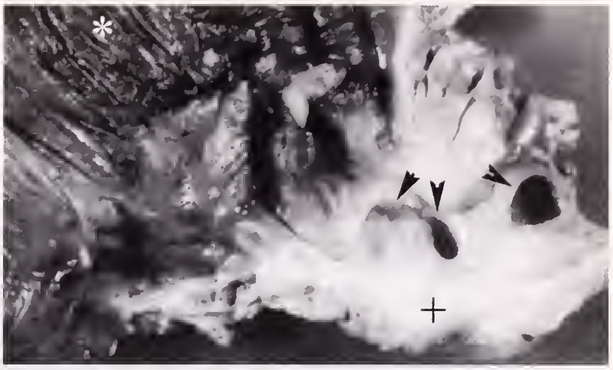

Fig. 2. Resected sigmoid colon demonstrating a markedly thickened wall (+) due to muscle hypertrophy. There is no sign of inflammatory change. Three wide-mouthed diverticula are visualized (arrowheads). The proximal colon (*) is markedly dilated.

Microscopic examination showed no significant inflammation within or adjacent to the diverticula (Fig. 3). The inner circular muscle layer of the external muscularis was markedly hypertrophied, accounting for the very unusual thickening of the wall seen with the naked eye. On gross examination, the mucosa appeared atrophic. Microscopic examination of the dilated segment showed healed colitis, possibly secondary to ischemia. No fibrosis of the wall of the stenosed segment was seen and no evidence of neoplasia was documented.

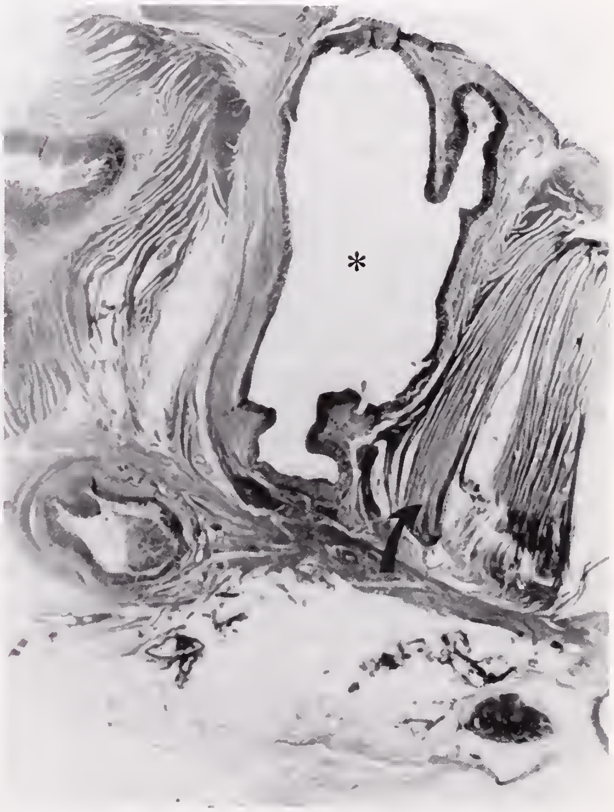

Fig. 3. Histology of sigmoid stricture: Enormous thickening of smooth muscle in the wall (curved black arrow). A large diverticulum (*) is visualized. There is no inflammation.

Discussion

In 1952, Celio (6) described the abnormal colonic involvement in specimens of patients with diverticulitis and drew comparisons between this myopathy and that observed in infants with hypertrophic pyloric stenosis. Following these initial observations, Morson (2) reported on four specimens of sigmoid colon removed for presumed diverticulitis, which showed abnormal muscle thickness of the sigmoid wall without any detectable diverticula or inflammation. The muscle abnormality appeared strikingly similar to that seen in patients with diverticulosis. Based on these findings, he suggested that the muscle thickening may be a predisposing factor in the development of diverticula. Cassano and Torsoli (7) first reported two cases of idiopathic muscular strictures of the sigmoid colon in humans, which bore striking similarities to the pathological picture seen in patients with diverticular disease.

The muscle abnormality of diverticular disease is characteristic (5). It is not seen in other inflammatory disease of the colon, whether segmental or diffuse. The underlying abnormality is shortening of the involved segment, most often the sigmoid. This results in large part from spasm and increased thickness of the taenia coli. The shortening explains several of the histological features which have been noted. These include thickening of both circular and longitudinal muscles without evidence of hypertrophy or hyperplasia, redundant mucosal folds, excess neural and vascular elements, and increased serosa and pericolic fat (8, 9). The belief that the muscle abnormality was central to the development of symptomatic diverticulitis led a number of authors in the 1960s and 1970s to propose sigmoid myotomy as a potential solution, and a number of patients underwent this procedure with symptomatic improvement (3, 4, 10).

Morson and Whiteway (1) described the thickened taenia coli as unusually firm and almost cartilaginous in consistency. They found that the circular muscle, which possesses an accordion-like appearance, was "so thick that it appeared as if the contractions had either fused or become calcified."

While some degree of colonic obstruction is observed in about two thirds of patients with acute diverticulitis, it is usually partial in nature and related to the inflammation, spasm and edema that commonly accompany this condition. Complete bowel obstruction due to diverticular disease is very seldom seen and rarely requires emergency surgery (5). It is usually the result of abscess formation with encroachment of the colonic lumen, or repeated episodes of diverticulitis with subsequent fibrosis and stenosis (11). In some instances, the clinical presentation is due to small bowel adherence to the inflammatory process rather than large bowel obstruction (5).

It is rare for muscle thickening to be so severe as to lead to large bowel obstruction, as occurred in our patient, with no evidence of acute inflammation, ischemia, fibrosis or neoplasm present. It would seem likely that the patient's psychiatric illness was responsible for the delay in seeking medical treatment and permitted aggravation and progression of the muscle abnormality in the sigmoid. Then, when acute large bowel obstruction occurred, medical attention became a matter of urgency.

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Hepatocellular Carcinoma with Fibrolamellar Pattern in a Patient with Autoimmune Cholangitis

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Abstract

A 75-year-old woman with a 15-year history of autoimmune cholangitis underwent orthotopic liver transplantation because of progressive liver decompensation. A clinically unsuspected hepatocellular carcinoma was found. A portion of the tumor showed fibrolamellar differentiation. Hepatocellular carcinoma, either with the usual pattern or with a fibrolamellar pattern, is rare in the setting of primary biliary cirrhosis, but has been seen in the setting of autoimmune hepatitis. Autoimmune cholangitis is a relatively recently recognized form of autoimmune liver disease whose association with hepatocellular carcinoma has yet to be determined. **Key Words:** Autoimmune cholangitis, primary biliary cirrhosis, hepatocellular carcinoma, fibrolamellar hepatocellular carcinoma.

Introduction

In recent years, there has been recognition of "autoimmune cholangitis" (AIC) as a new variant of autoimmune liver disease serologically indistinguishable from type 1 autoimmune hepatitis, often with high titers of antinuclear antibodies (ANA). Autoimmune cholangitis has the clinical, biochemical, and histologic features of primary biliary cirrhosis (PBC), but without demonstrable antimitochondrial antibodies (AMA) (1–3). Liver biopsies from these patients show the bile duct damage characteristic of PBC and may also show granuloma formation. Patients with this condition have previously been designated as having "atypical PBC" or "AMA-negative PBC." Some consider that this entity is unique (4), while others believe it controversial (5). Patients with autoimmune cholangitis, like patients with autoimmune hepatitis (6), appear to be more responsive to corticosteroid therapy than patients with PBC. The response to ursodeoxycholic acid has been shown to be similar in both AMA-positive and AMA-negative PBC (7).

Primary biliary cirrhosis was first described by Addison and Gull in 1851 (8) and then by Hanot in 1892 (9), but only became well recognized as a distinct disease entity in the 1950s and 1960s (10–12). Primary biliary cirrhosis is a disease typically of middle-aged women who present with the slow onset of cholestasis (13). The diagnosis of PBC is based on the findings of elevated serum alkaline phosphatase values indicative of bile duct destruction, increased levels of immunoglobulin M (IgM), increased titers of antimitochondrial antibodies, and histological evidence of bile duct injury and associated portal inflammation (14). In its early stages, as is well known, the name "cirrhosis" is incorrect, since the development of fibrosis and regenerative changes of hepatocytes does not occur for five or more years after the onset of disease (14, 15). The development of hepatocellular carcinoma in the setting of PBC has been thought to be exceedingly rare (16–21). Recently, however, an inci-

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dence of 6% has been reported in a study of 123 patients (22). In some patients with PBC, hepatitis C virus has been implicated as a potential co-carcinogenic factor (23).

Clinical studies (1 – 4, 6) and response to therapies (5 – 7) have shown that autoimmune cholangitis is a separate entity. In addition, recent studies have shown that the T-cell lymphocyte inflammatory cell infiltration in autoimmune cholangitis is distinct from that of both the usual form of autoimmune hepatitis and of PBC (24).

We had the opportunity to study the liver from a patient with autoimmune cholangitis who underwent orthotopic liver transplantation. A clinically unsuspected hepatocellular carcinoma was found in which there was a distinctly unusual histologic pattern. To the best of our knowledge, there has not been a previously reported case of hepatocellular carcinoma arising in the setting of autoimmune cholangitis.

Case Report

A 75-year-old Hispanic woman first developed clinical evidence of liver disease in 1981, at the age of 60, when she presented with pruritus and jaundice. The patient was reported to have detectable ANAs at significant levels, no detectable AMAs, and a liver biopsy consistent with PBC. Unfortunately, these studies were not available for review. Other laboratory test results were similarly not available. Her liver disease remained stable until 1995, when she had manifestations of progressive liver decompensation, with ascites, peripheral edema, increasing jaundice, and fatigue. The serum bilirubin value was 10.9 mg/dL, and reduced synthetic function was evidenced by a serum albumin value of 2.5 g/dL. At this time the ANAs were only demonstrable at a titer of less than 1:40, and AMAs were not unequivocally demonstrable. The α-fetoprotein value was 8.5 ng/mL. There was, however, no evidence of hepatic encephalopathy, and varices were not seen endoscopically. Imaging studies confirmed the presence of cirrhosis and did not identify a tumor. The patient underwent orthotopic liver transplantation in June 1996. Her post-operative recovery and subsequent course were uneventful and she was well eight months after transplantation.

Pathology

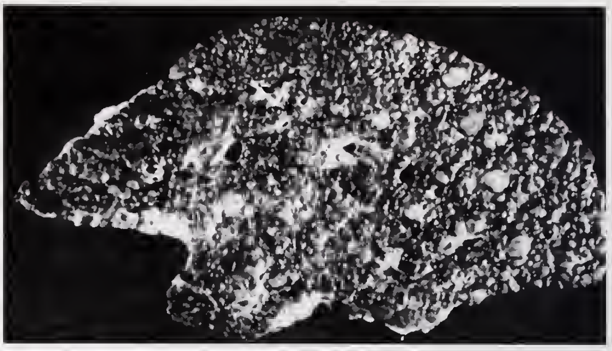

Fig. 1. Photograph of explanted liver showing macronodular cirrhosis with multiple macroregenerative ("dysplastic") nodules.

The explanted liver weighed 1440 grams and showed a deeply cholestatic macronodular cirrhosis (Fig. 1) with a few regenerative nodules greater than 1 cm in diameter (macroregenerative nodules [MRNs]) (Fig. 2).

The typical histologic features of the cirrhotic stage of PBC were seen, with marked paucity of bile ducts and without the early lesions characteristic of PBC (10). Regenerative nodules of varying size and shape were separated by broad fibrous septa in which there was marked chronic inflammation, as evidenced by infiltration of mostly lymphocytes and some plasma cells. The paraseptal rim of hepatocytes showed hydropic change of the cytoplasm with distinct bile stasis (i.e., "cholate stasis" or "feathery degeneration"). One of the 1.2 cm macroregenerative nodules consisted almost entirely of well- to moderately well-differentiated hepatocellular carcinoma (Fig. 3a). The most peripheral portion of the tumor showed the pattern of fibrolamellar hepatocellular carcinoma (Fig. 3b), with large, polygonal, slightly granular, eosinophilic malignant hepatocytes having large nuclei with prominent nucleoli. Tumor cells in this area were arranged in trabecula and separated by lamellar strands of relatively thin collagen fibers. Tumor cells reacted with antibody to α-1-antitrypsin and α-1-antichymotrypsin, but not to α-fetoprotein. There was neither vein invasion nor evidence of metastasis.

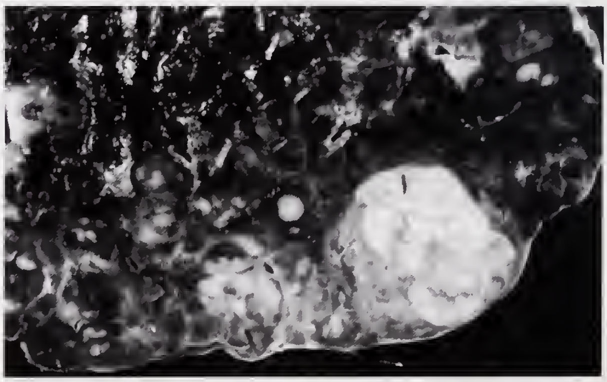

Fig. 2. Photograph of macroregenerative nodule which contained hepatocellular carcinoma.

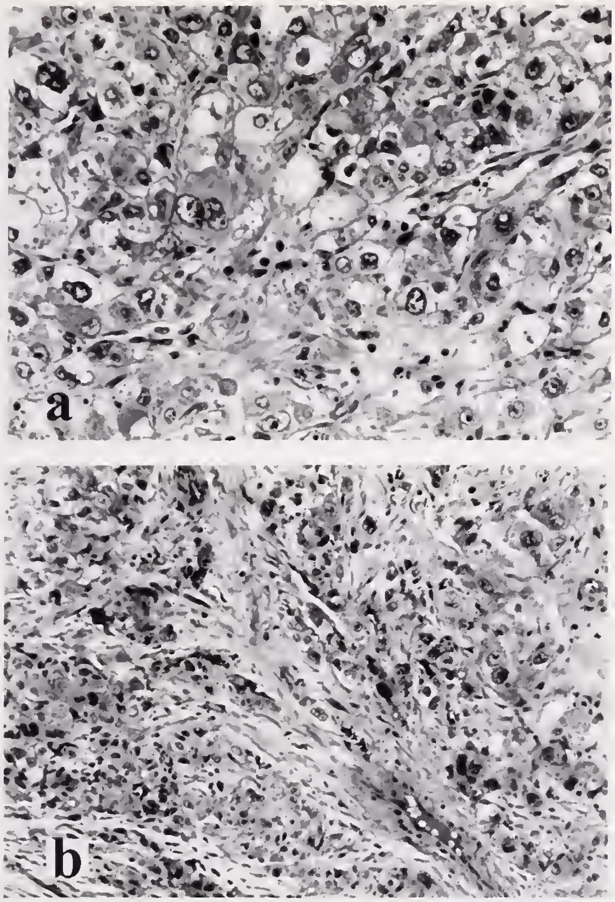

Fig. 3. a. Photomicrograph showing typical hepatocellular carcinoma arising in a macroregenerative nodule (Hematoxylin-eosin, x200). b. Photomicrograph of subcapsular portion of hepatocellular carcinoma showing features of fibrolamellar carcinoma (Hematoxylin-eosin, x100).

Discussion

Hepatocellular carcinoma is a well-known complication of cirrhosis (16, 21). It is prevalent in patients with cirrhosis due to hepatitis B (16, 25–29) and C (27–31), but is also well known to occur in the setting of hemochromatosis (16, 21, 32), α-1-antitrypsin deficiency (33), tyrosinemia (34), as well as other conditions (16, 21). Alcoholic liver disease is often complicated by the development of hepatocellular carcinoma, but in many patients the direct etiology may be unclear (16, 21, 35). In addition, hepatocellular carcinoma has been reported in patients with autoimmune hepatitis (36, 37), although it has recently been suggested that hepatitis C might be a contributing factor for at least some of these patients, since antibodies to hepatitis C can be found in some patients with autoimmune hepatitis (38).

Although the concept of the macroregenerative nodule, also known as "adenomatous hyperplasia," has only recently been widely accepted (39–43), the concept of hepatocellular carcinoma arising in the setting of the larger nodules of a macronodular cirrhosis is well known (44). Progression of the regenerative nodule in cirrhosis may lead to the formation of macroregenerative nodules, or alternatively, macroregenerative nodules may arise *de novo* as "dysplastic nodules" (45). Macroregenerative nodules are commonly seen in the cirrhotic stage of PBC (46), and are more likely to be sites of liver cell dysplasia and early changes of hepatocellular carcinoma (40–42). In our patient, there were multiple macroregenerative nodules, one of which had unequivocal hepatocellular carcinoma.

Fibrolamellar carcinoma is a variant of hepatocellular carcinoma, with distinctive histological and clinical features (47), including large eosinophilic cells arranged in trabecula that may be thin or thick and that are separated by fibrous bands imparting a lamellated appearance. Ordinary hepatocellular carcinoma can have significant fibrosis and can resemble fibrolamellar carcinoma (48), but in the usual case, the tumor cells of hepatocellular carcinoma do not have as much cytoplasm and there is generally considerable variation in nuclear and nucleolar size. In our case, the area of the tumor illustrated in Fig. 3b is indistinguishable from a typical case of fibrolamellar carcinoma, with large tumor cells separated by laminated collagen. In our experience, this pattern of hepatocellular carcinoma is quite unusual and is distinct from that of sclerosing hepatocellular carcinoma. The area with the fibrolamellar pattern did not represent the infiltrative edge of a usual hepatocellular carcinoma, where considerable reactive sclerosis might be seen, since it was entirely contained within the macroregenerative nodule.

The frequency of occurrence of hepatocellular carcinoma in the setting of autoimmune cholangitis is unknown. Autoimmune cholangitis is a relatively recently recognized disorder, the nature of which is still somewhat controversial. In the patient with long-standing autoimmune hepatitis, the incidence of hepatocellular carcinoma may be relatively high (36). In contrast, hepatocellular carcinoma is uncommon in PBC (16–22).

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Cytomegalovirus Infection in Patients with HIV Infection

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Abstract

Cytomegalovirus (CMV) is responsible for the most common viral opportunistic infection in persons with acquired immunodeficiency virus syndrome (AIDS). Clinical disease due to CMV has been recognized in up to 40% of patients with advanced HIV disease. The most common presentation is retinitis, although colitis, esophagitis, pneumonitis and neurological disorders are also reported frequently.

CMV retinitis is usually diagnosed clinically, and serological testing for CMV immunoglobulin is useful to support the diagnosis. Parts of the gastrointestinal tract (esophagus and colon) are the most common extraocular sites of CMV infection in AIDS patients.

Therapy with systemic agents, including intravenous ganciclovir, intravenous foscarnet, and intravenous cidofovir, is effective. Ganciclovir is associated mainly with hematological toxicity, while foscarnet and cidofovir are nephrotoxic. Intravitreal injections with these antiviral agents are also effective, but inconvenient, and there is a need for repeated injections. Intraocular implants that slowly release ganciclovir have been effective for both acute therapy and long-term maintenance, but the occurrence of contralateral ocular and extraocular disease is a serious concern. New agents, as for example an anti-sense agent against CMV, appear promising. **Key Words:** Cytomegalovirus infection, human immunodeficiency virus, CMV retinitis, CMV colitis, AIDS.

Epidemiology

Cytomegalovirus (CMV) causes the most common viral opportunistic infection in persons with acquired immunodeficiency syndrome (AIDS). Clinical disease due to CMV has been recognized in up to 40% of patients with advanced HIV disease (1–3). The most common presentation is retinitis, although colitis, esophagitis, pneumonitis and neurological disorders are also reported frequently.

CMV is a double-stranded DNA virus in the herpesvirus family. In HIV-infected persons, as with most herpes infections and other opportunistic infections associated with HIV infection, CMV disease is due to reactivation of the latent virus in a previously infected host. Seroprevalence of CMV ranges from 30–100%, depending on the population surveyed. The presence of CMV antibody in the male homosexual population is higher than in the male heterosexual population and more common with persons of lower socioeconomic status (4, 5). Almost 100% of homosexual men with HIV infection have serologic evidence of either recently acquired or reactivated CMV infection (1).

Despite the high prevalence of CMV antibody in HIV infection, the clinical manifestations of CMV disease do not generally present until the CD4 count drops below 100 CD4 cells/mm^3 (3, 6). In a study of 31 persons with HIV-infection and CMV retinitis, the mean CD4 count was 29 cells/mm^3 and the median was 17 cells/mm^3 (7). A multicenter observational cohort study of 1002 HIV-infected persons with fewer than 250 CD4 cells/mm^3 who were receiving zidovudine showed that disease due to CMV developed in 109 persons (8). Kaplan-Meier estimates of the proportion of persons who developed CMV dis-

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ease were 21.4% at 2 years for persons entering the study with fewer than 100 CD4 cells, and 10.3% for persons with initial counts greater than 100 cells/mm^3. Of the 109 persons developing CMV disease, 93 (85.3%) were diagnosed with retinitis, 10 (9.2%) with esophagitis, 3 (2.7%) with both retinitis and esophagitis, 8 (7.3%) with colitis, and 1 each with gastritis, hepatitis, and encephalitis.

CMV Retinitis

CMV retinitis is the most common ocular infection in AIDS and is an important cause of morbidity. With better treatment of the primary HIV infection, prophylaxis against *Pneumocystis carinii* pneumonia, and a resultant longer survival, the prevalence of CMV retinitis appears to be increasing (9).

Patients may present with symptoms of blurred vision, a scotoma or dark area covering part of the visual field, light flashes, or floaters. However, a significant percentage of infected patients are often asymptomatic despite the presence of extensive or vision-threatening CMV retinitis. In one study, fewer than 50% of AIDS patients with CMV retinitis had visual symptoms (10). Other studies have estimated that about 5% of visually asymptomatic AIDS patients have CMV retinitis (11, 12). Therefore, periodic ophthalmologic examination utilizing indirect ophthalmoscopy should be performed in those patients with CD4+ lymphocyte counts below 100/mm^3. In addition, one study utilizing formal perimetry detected visual field defects in 70% of patients with CMV retinitis (13). This suggests that patients should check their own vision in each eye separately on a daily basis and report to their physicians at once any alterations in their field of vision. A self-screening chart designed for this purpose was found in one study to detect scotomas in 63% of patients with previously undiagnosed CMV retinitis (14).

Due to the difficulty and associated morbidity of obtaining retinal tissue for histopathological examination, the diagnosis of CMV retinitis is usually based on its distinct clinical appearance of retinal necrosis. This most commonly manifests as a whitish opacification of the retina with exudates and variable amounts of hemorrhage (15). The appearance of this lesion may vary depending upon the location and rate of disease progression. A granular appearance is more typical of lesions which begin in the peripheral retina or of more slowly progressive lesions. These lesions are more likely to give rise to symptoms of light flashes or floaters. Lesions initially involving or adjacent to the optic nerve and macula (sight-threatening lesions), as well as more rapidly progressive disease, tend to have a more fluffy and edematous appearance. These lesions are more likely to cause visual field defects or blurred vision. Associated edema or subretinal fluid involving the macula can cause blurred vision which is reversible with anti-CMV treatment. However, any vision loss or visual field defect due to direct involvement by the virus is usually permanent. As the lesions enlarge, they tend to follow the course of the retinal vessels, forming large, wedge-shaped areas of involvement. Where there is a large amount of associated hemorrhage, it may resemble a slice of "pizza with cheese and catsup" (Fig. 1). Patients with AIDS and CMV retinitis typically have minimal ocular inflammation.

However, recently (16) AIDS patients with CMV retinitis controlled by chronic maintenance therapy and treated with highly active antiretroviral therapy which includes protease inhibitors have been observed to develop uveitis, vitreitis, and macular edema in the involved eye. This is unaccompanied by any visible activity of CMV retinitis and responds variably to topical anti-inflammatory agents or corticosteroids. CMV retinitis did not reactivate in the 2 patients treated with oral or periocular corticosteroids. This may represent an enhanced immune response to CMV.

About half the cases of CMV retinitis are bilateral at presentation (17), and if untreated about 60% of initially unilateral cases become

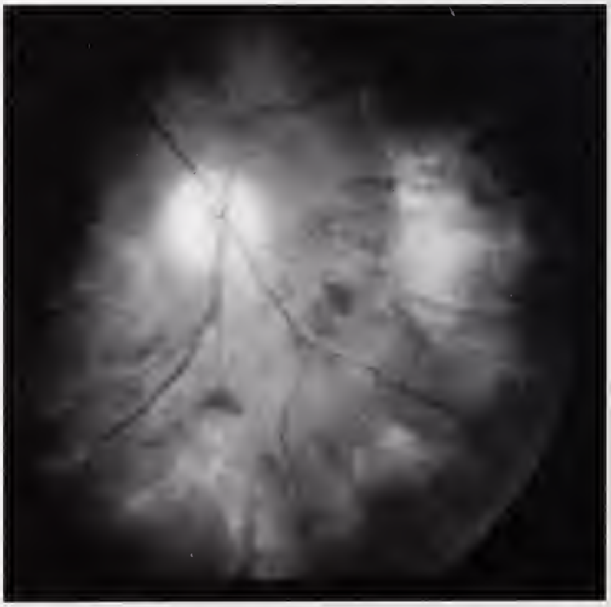

Fig. 1. CMV retinitis showing vascular sheathing. Along the vessel arcade, there is also edema and subretinal hemorrhage.

bilateral (18). The presence of positive blood cultures for CMV is neither necessary nor sufficient to make the diagnosis of CMV retinitis. In one study, although all 24 patients had positive urine cultures for CMV at the time of diagnosis of CMV retinitis, only 15 of 24 (63%) had positive blood cultures (6). However, serology to CMV-IgG should be positive in all patients; retinitis in a CMV-seronegative individual is unlikely to be due to CMV.

Other entities may mimic CMV retinitis. Cotton-wool spots are microinfarcts of the retinal nerve fiber layer that occur commonly in persons with HIV infection (19). These lesions do not affect vision and spontaneously regress over several weeks. A near absence of hemorrhage or unusually rapid progression is more typical of progressive outer retinal necrosis (PORN) due to varicella-zoster virus (20). Intraocular lymphomas may present as retinochoroidal infiltrates, optic nerve head swelling and vascular sheathing. *Toxoplasma* chorioretinitis is usually associated with a moderate-to-severe inflammation in the vitreous (21). However, atypical cases with minimal inflammation can occur in AIDS. *Pneumocystis carinii* chorioretinitis appears as discrete multifocal, white-yellow, choroidal lesions with no inflammation (Fig. 2) (22).

Despite appropriate antiviral treatment, up to 20–30% of patients with CMV retinitis may develop retinal detachments with a cumulative risk estimated to be 30–50% at one year (23, 24). Retinal detachments are more likely with larger areas of involvement of the peripheral retina and with continued activity of the retinitis (23–25). The detachments can often be anatomically repaired successfully with the use of vitrectomy techniques and the instillation of silicone oil, with retention of functionally useful vision. The long-term visual prognosis, however, is guarded (26–28).

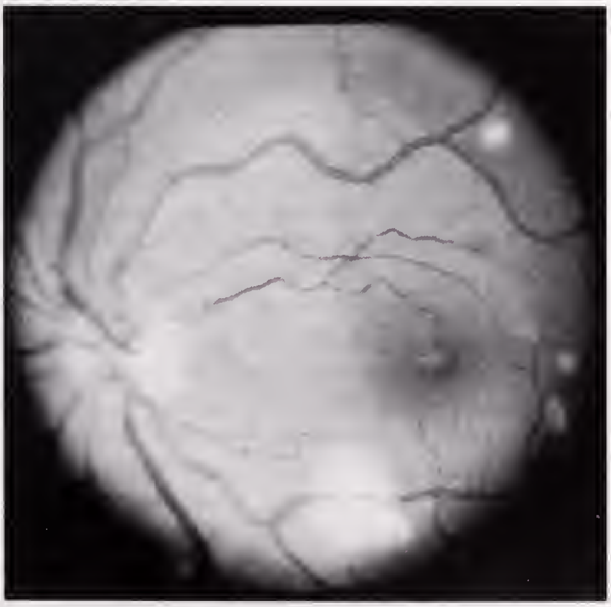

Fig. 2. *Pneumocystic carinii* retinitis.

CMV of the Gastrointestinal System

Gastrointestinal involvement with CMV is a significant problem in patients with AIDS. It is the most common extraocular manifestation of CMV infection in AIDS patients.

Involvement of the esophagus with CMV occurs in approximately 10% of persons with AIDS (29). The most common presentation is odynophagia, although the most common cause of odynophagia in persons with AIDS is *Candida* esophagitis.

The diagnosis of CMV esophagitis is made from the histopathological evidence of CMV with an inflammatory response in the appropriate clinical setting. The presence of extensive, large, shallow mucosal ulcers in the distal esophagus is the classical sign of the disease (30). Histopathologically, large intranuclear inclusion bodies can be seen in the epithelial cells at the edge of the ulcer.

Esophagitis may result from infections due to *Candida*, herpes simplex, histoplasmosis, human immunodeficiency virus, *Mycobacterium tuberculosis* and rarely *M. avium-intracellulare* complex, and *Pneumocystis carinii*, as well as reflux or peptic ulcer disease and lymphoma (31). Due to the prevalence of *Candida* esophagitis in this population, one can treat esophageal symptoms empirically, especially in the presence of oral thrush, with ketoconazole or fluconazole, and endoscope only those persons who fail to respond.

CMV colitis can occur in up to 10% of persons with AIDS (8). Diarrhea, abdominal pain, fever, weight loss and anorexia are frequently present. Extensive gastrointestinal hemorrhage and perforation can also occur. The radiographic manifestation of CMV colitis is nonspecific and may mimic the findings of other inflammatory bowel conditions, including ulcerative colitis (31).

Evaluation in this group of patients should also include flexible sigmoidoscopy or colonoscopy with biopsy and culture. One should exclude other gastrointestinal pathogens such as *Cryptosporidium, Microsporidian, Giardia lamblia, Entamoeba histolyticum, Salmonella, Shigella, Campylobacter, Yersinia, Mycobacteria,* and *Clostridium difficile*. In addition, lymphoma, Kaposi's sarcoma, and inflammatory bowel disease must be considered.

Although CMV involvement of the liver and biliary tract is often noted only at autopsy, hepatitis proven clinically to be secondary to CMV is rare in persons with HIV infection (1). Biliary tract or hepatic involvement by CMV may present with right upper quadrant pain and elevated alkaline phosphatase, mimicking infection with *M. avium-intracellulare* complex and *Cryptosporidium*.

Pancreatitis in HIV-infected persons is noted to be increasing in frequency. CMV has been found to be the most common viral agent associated with this condition (28–34). The presentation is similar to other forms of pancreatitis, i.e., abdominal pain, nausea, vomiting, cachexia, abdominal tenderness, and hypoactive bowel sounds. However, some of these patients may have only a mild increase in amylase and a marked increase in lipase (34).

CMV Pneumonitis

CMV is seldom implicated ante mortem as an isolated pathogen causing pneumonitis in persons with HIV infection (35), but CMV is a common cause of interstitial pneumonitis in immunocompromised patients, especially patients with bone marrow transplant. Murray et al. (35) studied a large group of AIDS patients with active symptomatic pneumonitis. Seventeen per cent were found to have CMV by culture. Two-thirds of these, however, had coexistent *Pneumocystis carinii* pneumonia (PCP) and only 4% had CMV as the sole pulmonary pathogen (36). Recently, Jacobson et al. (37) found that the morbidity and mortality of coexisting CMV infection with PCP were comparable to that of PCP and do not adversely affect the prognosis of PCP in AIDS since CMV is frequently isolated from bronchoalveolar fluid and lung tissue.

Clinical presentations of CMV pneumonitis have ranged from asymptomatic viral shedding to rapidly fatal pneumonia. An interstitial pneumonitis with fever, dyspnea, dyspnea on exertion, nonproductive cough, and hypoxemia is most commonly noted. Diagnosis of CMV pneumonitis should only be made by histological identification of multinucleated CMV inclusion bodies in lung tissue, and other pulmonary pathogens, such as *P. carinii, M. tuberculosis, Histoplasma capsulatum, Coccidioides immitis, Cryptococcus neoformans, Streptococcus pneumoniae* and *Hemophilus influenzae*, should be excluded.

CMV Neurological Diseases

In autopsy studies, CMV disease in the central nervous system has been found in 25% of persons with HIV infection (38–41). Pathological diagnosis is based on finding typical inclusion bodies, or by immunohistochemical or *in situ* hybridization techniques. Pathologic findings are: necrotizing lesions with microglial nodules, focal parenchymal necrosis, necrotizing ventriculoencephalitis, and radiculomeningomyelitis.

Clinically neurologic syndromes caused by CMV in AIDS are usually unrecognized. Encephalitis (38–40), polyradiculoneuritis (42) and peripheral neuropathy (43) have been reported. A polyradiculoneuritis due to CMV has been recently identified as a progressive polyradiculoneuropathy associated with distinct cerebrospinal fluid abnormalities, including a predominantly polymorphonuclear pleocytosis and hypoglycorrhachia (44).

It is noteworthy that a recent autopsy study showed that 42% of patients with CMV retinitis had CMV encephalitis, with the prevalence of encephalitis increasing to 75% if the retinitis was adjacent to or involved the optic nerve. And 91% of those with CMV encephalitis had CMV retinitis (45). Therefore, an ophthalmologic evaluation is indicated in AIDS patients with CMV encephalitis and may be of diagnostic value in AIDS patients with neurological symptoms.

Diagnosis of CMV Diseases

As mentioned earlier, most CMV diseases are diagnosed by histological biopsy, except retinitis, which is diagnosed by clinical observation in conjunction with serodiagnosis or culture and clinical setting.

The most common method currently used to detect CMV is either by culture or by the more rapid modification of this procedure called the shell-vial method (46). However, these detection methods have limitations. Cultures require fresh samples and may take up to several weeks to provide a reliable answer. The shell-vial method may be faster, usually requiring 48 hours. However, because they are time-consuming procedures and correlate poorly with clinical disease, these assays are not generally used as part of the management of clinical CMV disease.

Newer methods for detection of CMV viremia have been developed, such as polymerase chain reaction (PCR) (47) and detection of antigen pp65 by the antigenemia test in peripheral blood polymorphonuclear leukocytes (48).

Earlier results have shown that both methods are useful in predicting development of CMV disease up to several months prior to clinical disease. Qualitative plasma CMV DNA has a high sensitivity (89%) and good specificity (75%) for predicting development of CMV disease; pp65 antigenemia uses monoclonal antibodies against a lower-matrix phosphoprotein (pp65) of the CMV (48). Measurement is technician-dependent and, therefore, standardization between laboratories may be difficult. Dodt et al. (49) have demonstrated that CMV serology has no predictive value. The PCR test has detected CMV DNA a median of 46 days before the onset of disease. This was earlier than the 34 days median time for the antigenemia test and a median of 1 day for CMV blood cultures. Multivariate analysis showed that the PCR method is superior to other tests (odds ratio: CMV PCR 10.0, antigenemia test 4.4 and CMV cultures 4.3) (49).

Shinkai et al. (50) compared the results of culturing CMV from plasma and urine with that of determining the plasma PCR in 99 patients. They found that the plasma PCR was superior to culture for identification of AIDS patients at risk for CMV disease, and that quantitation of plasma DNA further identifies high-risk persons.

Branched DNA signal amplification for CMV viral load is in development. Earlier results showed that it can quantify CMV very accurately, but lacks sensitivity in the lower range (51).

Treatment

Ganciclovir

Ganciclovir (DHPG) is a nucleoside analog which inhibits herpes virus DNA polymerase. Its action depends on phosphorylation in CMV-infected cells. Most strains of CMV resistant to ganciclovir are unable to phosphorylate ganciclovir. The drug is virustatic against CMV. Thus, when treatment for disease is stopped, viral spread and progression of disease characteristically recur (3).

In uncontrolled trials, treatment with ganciclovir resulted in the improvement or stabilization of CMV retinitis in 80–90% of patients (52). The median time to clinical progression could be as long as 145 days from the diagnosis of CMV retinitis, while continuing some maintenance therapy with ganciclovir.

However, in a randomized, controlled trial comparing ganciclovir with delayed therapy using strictly graded photographic endpoints, progression of retinitis while on ganciclovir occurred in a median of 50.5 days, compared with the progression on delayed therapy, which occurred in a median of 15 days (53). Similarly, the results of the Studies of the Ocular Complications of AIDS (SOCA) demonstrated the median time to progression of CMV retinitis while on ganciclovir was 56 days (54).

Although the efficacy of ganciclovir for CMV gastrointestinal infection in AIDS patients is less well documented, therapeutic trials utilizing dosing regimens similar to that for retinitis showed good clinical responses. However, unlike the situation with CMV retinitis, because the cells lining the gastrointestinal tract regenerate rapidly, therapy can often await development of moderate-to-severe symptoms in order to justify the use of toxic systemic therapy. Likewise, there is no consensus that maintenance therapy is necessary or beneficial, especially since the risk of development of resistant CMV increases with maintenance therapy (55, 56).

The utility of ganciclovir therapy in the treatment of CMV pneumonitis is anecdotal. In bone marrow transplant recipients, the combination of ganciclovir with high-dose-intravenous immunoglobulin has been shown to be more effective. This experience appears not to be the case in persons with AIDS (57).

Neutropenia and thrombocytopenia are the major dose-limiting toxicities of ganciclovir therapy. Because ganciclovir and zidovudine are both myelosuppressive, it is difficult to administer these agents concurrently. However, this problem has been ameliorated by the availability of non-myelosuppressive antiretroviral agents such as didanosine (ddI), zalcitabine (ddC) and stavudine (d4T) and by the use of granulocyte growth factors (e.g., G-CSF and GM-CSF).

Intravitreal injections of ganciclovir have been used for treatment of CMV retinitis in persons unable or unwilling to tolerate systemic therapy with ganciclovir or foscarnet (58, 59). Concentrations greater than the ID_{50} for most strains of CMV can be maintained for 60 hours after a single 200 μg injection (59). Two injections of 200–400 μg per week are normally given for 2–3 weeks during an induction period, followed by weekly maintenance injections. The dosages appear equally effective without clinically apparent toxicity. This method appears to be about as effective as intravenous therapy. One group has used repeated intravitreal injections of 2 mg of ganciclovir in conjunction with intravenous therapy, with no evidence of toxicity (60). Inadvertent injection of 40 mg did result in severe retinal toxicity (61).

An implantable intraocular device that allows the slow, sustained release of ganciclovir to the vitreous over 6–8 months has been developed (Fig. 3). Twenty-six patients (30 eyes) with CMV disease limited to the peripheral retina were randomized to receive immediate treatment with this device, or to observation with deferred implantation of the device when the retinitis progressed (62). The median time to progression was 15 days in the deferred group versus 226 days in the immediate treatment group. Ultimately, 39 eyes received implants. The time to progression was much longer with the intraocular device than that experienced with systemic therapy in the SOCA study. However, the lack of systemic therapy increases the risk of CMV disease in other organs as well as in the second eye by 50% at 6 months.

A larger randomized trial compared an implant delivering 1 µg/hour, an implant delivering 2 µg/hour, and intravenous ganciclovir in AIDS patients with newly diagnosed CMV retinitis (63). The median time to progression with each implant (221 days and 191 days respectively) was significantly longer than with intravenous (IV) ganciclovir (71 days). However, the risk of second eye involvement was only half as great with IV therapy. Similarly, patients receiving IV therapy were less likely to develop extraocular CMV (0% vs 10.3% in the implant groups). Thirty-one percent (31%) of the implanted patients developed biopsy-proven visceral disease, and CMV disease was present in 3 out of 4 additional patients at autopsy. At least one death was attributed to CMV. In comparison, systemic treatment in the SOCA study resulted in a 3–4% incidence of non-ocular CMV disease (64) and a 16–27% risk of second eye involvement (54). A second operation was performed on the patients who had the intraocular implant to replace the device once it was depleted of the drug. Nine eyes, however, developed progression of retinitis prior to the 32 weeks estimated to be the safe replacement time.

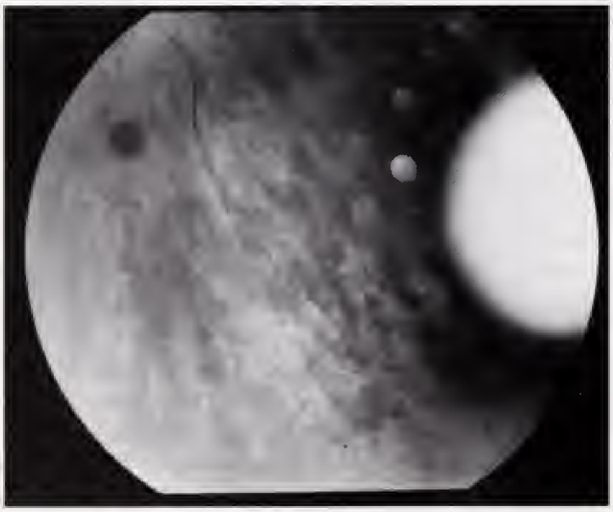

Fig. 3. Ganciclovir implant as observed through the lens. Opposite the implant, there is evidence of healing CMV retinitis.

Complications of retinal detachment, intravitreal hemorrhage, endophthalmitis, improper placement and damage to the lens have been reported (11–13, 58). In an effort to address the issues of systemic CMV and contralateral ocular involvement, a randomized controlled study was performed comparing an intravitreal ganciclovir implant (IGI) plus oral ganciclovir (1.5 grams three times daily) with an IGI plus oral placebo, and intravenous ganciclovir (65). The incidence of biopsy-proven CMV disease or CMV retinitis was 22.4%, 37.8%, and 17.9% respectively. Oral ganciclovir statistically significantly reduced the risk of new CMV disease compared to placebo. However, among the subgroup of patients receiving concomitant HIV protease inhibitor therapy, the incidence of new CMV disease was low and not significantly different between treatment groups. Overall, oral ganciclovir also reduced the incidence of new AIDS-associated conditions, particularly Kaposi's sarcoma.

As described above, an oral form of ganciclovir has become available recently. The bioavailability of ganciclovir administered orally with food averaged 9% (66). Daily doses of 3000 mg or more yielded average serum ganciclovir concentration exceeding 0.5 µg/mL (67), a concentration sufficient to inhibit most clinical isolates of CMV *in vitro* (68).

An open-label, randomized study in patients with AIDS and newly-diagnosed, stable CMV retinitis was performed comparing oral with IV ganciclovir (69). On the basis of the masked assessment of photographs from 115 subjects, the mean time to the progression of retinitis was 62 days in those given IV ganciclovir and 57 days in those given oral ganciclovir (p=0.63, RR=1.08). However, on the basis of fundoscopy by ophthalmologists who were aware of the subjects' treatment assignments, the mean time to progression was 96 days in subjects given IV versus 68 days in subjects given oral ganciclovir (p=0.03, RR=1.68). Survival and changes in visual acuity were similar in the two groups. The difference in mean time to disease progression was thought likely to be due to the bias of the ophthalmologists, who were more ready to reinduce or to switch therapy in those patients receiving the drug orally. However, it is also possible that the treating ophthalmologists could detect CMV retinitis in the peripheral retina that is unable to be photographed or may detect clinical progression that does not meet the photographic criteria for progression in the study. Furthermore, patients receiving the oral drug were more likely to develop lesions in the initially uninvolved eye than those receiving intravenous ganciclovir. It has also been noted that reactivation is more difficult to identify ("creeping scars") in patients receiving oral ganciclovir (70). Oral ganciclovir may therefore not be appropriate for patients with lesions close to the fovea or the optic disc. In spite of these shortcomings, oral ganciclovir was deemed to be safe and effective as maintenance therapy for CMV retinitis, and is more convenient for patients to take than is IV ganciclovir. There is recent evidence that a higher oral dosage, up to 2 grams tid, may be more effective for maintenance therapy (71).

Foscarnet

Foscarnet inhibits DNA polymerase and prevents chain elongation by blocking nucleoside binding sites of all herpesvirus. Specifically, it prevents the cleavage of pyrophosphate from adenine triphosphate and does not require phosphorylation for activation (3). In addition to its inhibitory activity against the herpes DNA polymerase (*herpes simplex* 1 and 2, VZV and CMV), foscarnet has activity against the reverse transcriptase of HIV (72, 73).

Like ganciclovir, foscarnet is only virustatic, and lifelong treatment of retinitis with this drug is required. The major toxicities of foscarnet are its effects on renal function and serum electrolytes, especially calcium. Prevention of nephrotoxicity has been minimized by concurrent infusion of IV saline solution. Frequent monitoring of serum creatinine, creatinine clearance, serum electrolytes, calcium and magnesium is required.

The efficacy of foscarnet was demonstrated initially in uncontrolled trials (73–76). Approval of foscarnet was largely based on the results of a randomized, controlled clinical trial conducted at the NIH (6). The results of the SOCA trial showed that foscarnet and ganciclovir are equally efficacious (54). However, patients who received foscarnet had a longer median time of survival. This was speculated to be secondary to the fact that most patients on ganciclovir were unable to take zidovudine and that foscarnet was active against HIV. However, differential zidovudine use could not fully explain these results. Furthermore, both drugs had a significant suppressive effect on circulating p24 antigen, with no statistical difference between the two drugs (77).

With increasing use of ganciclovir for prolonged periods of time, ganciclovir-resistant strains of CMV are becoming more frequently recognized (56). Foscarnet has been used successfully to treat CMV retinitis in patients with ganciclovir-resistant CMV (78). However, foscarnet-resistant CMV retinitis also occurs with prolonged therapy. Viral sensitivity testing may possibly be useful in helping to direct therapy in the future (79).

Intravitreal injections of foscarnet have also been used to treat CMV retinitis at a dosage of 1200 μg. Vitreous levels remain above the mean 50% inhibition value for CMV for about 56 hours (80). An induction regimen of 2 injections weekly for 3 weeks, followed by once-weekly maintenance injections, is recommended (80, 81). Although there is less experience than with intravitreous ganciclovir, the efficacy and toxicity appear to be comparable. A higher dosage of 2400 μg has been used successfully (79).

Clinical efficacy of foscarnet against gastrointestinal infections due to CMV has been reported. In a study involving 14 AIDS patients with CMV gastrointestinal infection who failed ganciclovir, Dieterich et al. (82) showed that substitution with foscarnet was effective in inducing remission.

The combination of ganciclovir and foscarnet has also been used to treat CMV infection in AIDS patients. Preliminary results demonstrated that simultaneous combination therapy for CMV retinitis is better than foscarnet or ganciclovir alone in patients with clinically resistant CMV retinitis (83–86). The CMV Retinitis Retreatment Trial sponsored by SOCA has recently been completed (87). Patients were randomly assigned to standard treatment with ganciclovir or foscarnet, or to combination therapy (ganciclovir, 5 mg/kg daily and foscarnet, 90 mg/kg daily). The results of the study showed that combination therapy produces a longer median remission (4.3 months) than either ganciclovir alone (2.0 months) or foscarnet alone (1.3 months) and less loss of visual field than with either monotherapy. However, the combination therapy did have a greater negative effect on quality-of-life measures.

The recommended maintenance dosage for foscarnet is either 120 mg/kg or 90 mg/kg once daily with adjustments for calculated creatinine clearance. However, there is evidence that the higher dosage is more effective in controlling CMV retinitis (87) and has greater survival benefit (88, 89).

Cidofovir

1-[(S)-3-hydroxy-2-(phosphonomethoxy) propyl] cytosine (HPMPC) or cidofovir, a nucleotide analog, has been found to be active against CMV. Being a nucleotide, it does not require phosphorylation in CMV-infected cells. The drug is unique because of its prolonged intracellular half-life (17 – 65 h) and prolonged *in vitro* and *in vivo* antiviral effects in animal models against CMV and herpes virus (90). Oral probenecid given in high doses before, during, and after infusion, as well as concomitant intravenous hydration, is necessary to prevent severe nephrotoxicity. In a controlled randomized study (Gilead study #107), patients received 5 mg/kg IV once a week for 2 weeks and then, by randomization, either 5 mg/kg or 3 mg/kg once every other week. Interim analysis of the first 60 patients found that the median time to retinitis progression was 115 days in the higher dose group and 49 days in the lower dose group. Creatinine elevation occurred in 2 patients in each group. Probenecid caused adverse reactions in 48% of the patients, with severe but reversible reactions in 2 (3%) (91). SOCA compared deferral of therapy in 64 previously untreated patients with small, peripheral retinitis lesions, to intravenous cidofovir 5 mg/kg with further randomization to a maintenance dosage of 3 mg/kg or 5 mg/kg every 2 weeks. The median time to progression in the low-maintenance dose group was 64 days compared to 21 days in the deferred group ($p=0.52$). The median time to progression was not reached in the high-maintenance dose group and was 20 days in the deferral group ($p=0.009$). Two cidofovir recipients developed persistent elevations of serum creatinine of more than 2.0 mg/dL (92).

In a randomized controlled study (Gilead #106) in patients with newly diagnosed CMV retinitis, IV cidofovir 5 mg/kg weekly for 2 weeks followed by maintenance every 2 weeks delayed the median time to progression from 22 to 120 days ($p<0.0001$). Twenty-four percent (24%) developed treatment-limiting nephrotoxicity. Probenecid side effects occurred in 56% but were dose-limiting in only 7% (93). Given better efficacy in the 5 mg/kg group and the fact that toxicity was comparable to that of the 3 mg/kg group, the dose of choice for maintenance treatment is 5 mg/kg every other week.

It recently has been recognized that iritis may occur in about one-fourth of patients receiving intravenous cidofovir, with a cumulative incidence of 50% after 125 days of therapy (94). Ocular hypotony may also occur as a complication of IV cidofovir (94, 95).

Prevention

Since CMV infection is a major cause of morbidity and mortality in late-stage HIV infection (CD4 < 100), therapeutic strategies to prevent CMV infection in this group become meaningful.

A double-blind, placebo-controlled study reported by Spector et al. (96) showed that oral ganciclovir (1000 mg 3 times daily) was beneficial in patients with CD4 lymphocyte counts less than 100/mm^3 (study #1654). At entry into the study and every 2 months thereafter, ophthalmologic examinations were performed and viral cultures were obtained. The rate of dissemination of CMV disease (primarily CMV retinitis) among 725 patients was 39% in placebo recipients compared with 20% in those who received oral ganciclovir ($p=0.001$). There was also a trend in ganciclovir recipients toward a survival benefit at 18 months (37% in the ganciclovir group and 45% of the patients in the placebo group had died), but this was not statistically significant ($p=0.13$).

A conflicting result on the effectiveness of oral ganciclovir for CMV prophylaxis was reported from the NIH-sponsored Community Programs for Clinical Research on AIDS (CPCRA) (97). In this study, patients with CD4 counts less than 100 cells/mL were eligible. As in study #1654, the endpoint was development of CMV disease. In contrast to study #1654, there was no significant difference between the ganciclovir arm and the placebo arm in the proportion of patients who died or developed CMV disease.

The difference in the results of the two studies can be explained perhaps by differences in study design, drug exposure, and study population. In study #1654, ophthalmologic examinations were required at baseline and every 2 months thereafter, regardless of whether symptoms of retinitis were present. In the CPCRA study, baseline ophthalmologic examination was not required in the absence of symptoms. Follow-up examinations were performed only if symptoms were reported. Therefore, asymptomatic retinitis may not have been detected in the CPCRA study.

The duration of drug exposure also differed in the two studies. The median duration of treatment for the blinded portion of the CPCRA study was 7.2 months, versus 8.7 months for study #1654. Based on preliminary results favoring treatment with oral ganciclovir, the Data and Safety Monitoring Board (DSMB) of the Division of AIDS (NIAID) recommended discontinuation of the placebo arm of study #1654. Shortly after, the DSMB recommended continuation of CPCRA 023, but study participants were offered the option of switching to treatment with oral ganciclovir.

The degree of immunosuppression of patients in the two studies also differed. Patients treated with oral ganciclovir in study #1654 had mean and median CD4 cell counts of 26 cells/μL and 21 cells/μL respectively, and 88% had CD4 cell counts of less than 50 cells/μL. In contrast, those in the CPCRA study had mean and median CD4 cell counts of 44 cells/μL and 35/μL, and 65% had CD4 cell counts of less than 50 cells/μL. Based on these demographic data, patients treated in study #1654 appear to have been more immunosuppressed and therefore were more likely to develop CMV disease. Consequently, the CPCRA study may not be powerful enough to bring out the differences between the groups.

Valaciclovir, a pro-drug of acyclovir, given as a high dose of 2 g by mouth, 4 times daily, was compared in a randomized trial to acyclovir given in a dose of either 400 mg by mouth, twice daily, or 800 mg by mouth, 4 times daily, for the prevention of CMV disease in CMV seropositive patients with CD4 count less than 100 mm^3 by the AIDS Clinical Trials Group (ACTG) (98). This study was terminated early because there was a trend of increased mortality in the valaciclovir arm (p=0.06). The reason for this trend in mortality is unknown. However, CMV disease occurred in 17.5% of acyclovir recipients and 11.7% of valaciclovir recipients (p=0.04).

New Developments

Intravitreal injection of cidofovir is also being studied in conjunction with oral probenecid. Doses higher than 20 μg have had unacceptable toxicity (mainly ocular hypotony). A single 20 μg injection appears to control CMV retinitis for about 2 months. There was some lowering of intraocular pressure, and a mild-to-moderate iritis developed in about 20% of eyes (99, 100). However, the formulation studied differs from that which is now available for intravenous use; the safe and effective dosage for intravitreal use has not been determined.

ISIS-2922 is a phosphorothioate anti-sense nucleotide complementary to CMV messenger RNA-encoding regulatory proteins. It is given only as an intravitreal injection once a week for 2–3 doses for induction and then every 2 weeks for maintenance. Ocular and systemic side effects were monitored immediately prior to the administration of each dose for the duration of treatment which exceeded 50 weeks in some patients. It has had apparent efficacy in patients intolerant of or unresponsive to intravenous ganciclovir or foscarnet, but can cause uveitis and a dose-related retinal toxicity (101).

Potentially more effective oral agents are also being tested. Valganciclovir is a pro-drug of ganciclovir. When given orally twice daily, valganciclovir has a bioavailability of 40%. It provides areas under the time/concentration curve of ganciclovir which are comparable to intravenous ganciclovir. Lobucavir is a new nucleoside analog with broad-spectrum *in vitro* activity against CMV and other herpes viruses, as well as HIV and hepatitis B viruses. Its oral bioavailability is 30–40% (102). The benzimidazole riboside compounds, 1263W94 (5,6-dichloro-2[isopropylamino]-1-β-L-ribofuranosyl-1H-benzimidazole) and BDCRB (5,6-dichloro-2-bromo-1-β-D-ribofuranosyl-1H-benzimidazole), are a new class of potent inhibitors of CMV replication. 1263W94 inhibits the accumulation of linear and high molecular-weight CMV DNA and is being tested in HIV-positive patients (103). BDCRB blocks a step necessary for packaging unit lengths of CMV DNA into the nucleoside. Neither of these drugs depends on the inhibition of the viral DNA polymerase, which makes them attractive alternative agents for drug-resistant strains.

Currently, new methods of treating HIV with combinations of highly active retroviral agents including protease inhibitors enable an improvement in immune function and CD4 count. Indirectly, these may also delay the development of CMV disease or prevent reactivation of CMV retinitis (104, 105). This clinical observation is intriguing, but a controlled clinical trial is needed to confirm this result. A caveat is that patients on highly active antiretroviral therapy may also develop CMV retinitis even if CD4 counts exceed 200 (106).

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The Importance of Peritoneal Imaging in the Workup of Genital Edema in Patients on Continuous Ambulatory Peritoneal Dialysis

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Abstract

Background: Genital edema is a well-reported complication of peritoneal dialysis. This phenomenon has been associated with extravasation of dialysate from the peritoneal cavity through a defect in the abdominal wall or through an inguinal hernia (or patent processus vaginalis, persistent sac). In the first case, fluid tracks through the soft tissues of the abdominal wall and settles in the dependent genitalia. In the second, fluid tracks through the inguinal hernial defect and infiltrates into the tissues distal to the defect. It is difficult to precisely diagnose the etiology of many of these cases but it is obviously important.

Method: We report a case of a patient who presented with penile and scrotal edema and was eventually found to have bilateral patent processus vaginalae. We used computed tomography and peritoneal scintigraphy in order to ascertain the diagnosis.

Results/Conclusions: We believe that computed tomography and peritoneal scintigraphy are extremely helpful in the workup of genital edema in patients on continuous ambulatory peritoneal dialysis. **Key Words:** Genital edema, continuous ambulatory peritoneal dialysis, complications, adverse effects, hernia.

Introduction

Continuous Ambulatory Peritoneal Dialysis (CAPD) has been shown to be useful in treating patients with chronic renal failure, and has many advantages over hemodialysis (1). Its most common and serious complication is peritonitis (2). Genital edema is reported more frequently. It can be an immediate or late complication of this form of dialysis. Penile and scrotal edema develop by either of two mechanisms (3). In the first, dialysate extravasates from the peritoneal cavity through the catheter insertion site or a ventral or incisional hernia; the fluid tracks through the soft tissues of the abdominal wall to settle in the dependent genitalia. In the second mechanism, fluid extravasates through an inguinal hernia of patent processus vaginalis (persistent sac) directly into the tunica vaginalis and surrounding tissues. Obviously, determining which one of these problems exists is vital to the proper treatment of the patient. We report a case in which a patient developed both scrotal and penile edema shortly after beginning CAPD. We learned to appreciate the difficulty in establishing a definitive etiology for this patient's genital edema and found peritoneoscintigraphy and computerized axial tomography with contrast material added to the peritoneal dialysate to be invaluable in our workup. We feel that at least one, and perhaps both, of these tests should be used to ascertain a diagnosis before surgical therapy is initiated.

Case Report

A 61-year-old white male with a past medical history of chronic renal failure due to diabetic nephropathy had a Cruz peritoneal dialysis catheter (Corpak Medsystems, Wheeling, IL) placed via an open lateral transrectus incision in an ambulatory setting without incident. Seven weeks later, after initiation of CAPD, the patient developed penile and scrotal edema. CAPD was withheld for a few days until the edema resolved. After resuming CAPD, the genital edema recurred.

Physical examination failed to reveal inguinal hernia or cough impulse. Examination of the catheter exit site and implantation incision failed to reveal evidence of leakage, hernia or subcutaneous fluid collection. There was no abdominal wall edema present.

The penile edema suggested to us that there was leakage from around the catheter as it passed through the abdominal wall. He was taken to the operating room for exploration. We were unable

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to demonstrate a leak or hernia by direct examination and intraoperative fluoroscopy. The catheter was removed and a new catheter was placed. Peritoneal dialysis was withheld for one week and when it was resumed, the problem recurred.

The patient was then reevaluated using CT scan and peritoneal scintigraphy. The nuclear study was performed using 7.6 mCi of ^{99m}Tc labeled albumin colloid mixed with 2 liters of dialysate which was then infused into the peritoneal cavity via the peritoneal dialysis catheter. The patient was scanned using a gamma camera, in anterior and oblique views. After 10 minutes, the isotope was seen to be present in the groin areas bilaterally, consistent with bilateral patent processus vaginalae (Fig. 1). After 2 hours, the dialysate fluid was drained from the peritoneal cavity and another scan was then performed (Fig. 2). Subsequently, 2 liters of dialysate, to which was added 100 mL of 60% diatrizoate meglumine contrast medium, was instilled into the peritoneal cavity. The patient went about his usual activities for one hour before undergoing CT scanning of his abdomen and pelvis using 10 mm slices from the xiphoid process to the symphysis pubis. This study also showed extension of the contrast material into bilateral patent processus vaginalae (Fig. 3). In neither of the two studies was contrast nor isotope seen in the soft tissues of the abdominal wall. CT scan did not demonstrate small bowel or other contents in either inguinal canal.

The patient underwent bilateral inguinal surgical exploration. A patent processus vaginalis was found on the left side. High ligation was performed and the floor was reinforced with marlex mesh. On the right side, a patent processus vaginalis (persistent sac) and floor weakness were identified. High ligation and a modified Bassini repair were done. There were no cord edema, tears, or leaks identified in the hernias or patent processus.

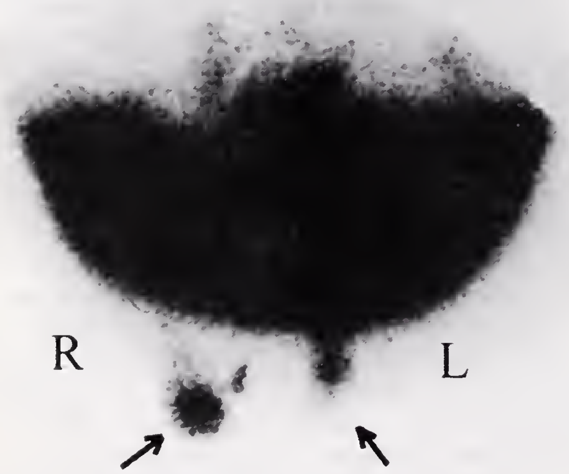

Fig. 1. Peritoneal dialysis fluid, to which a radioisotope has been added, has been instilled into the abdomen. Fluid is evident in both inguinal canals and in the right hemiscrotum (arrows) at 10 minutes in this anterior view of the pelvis.

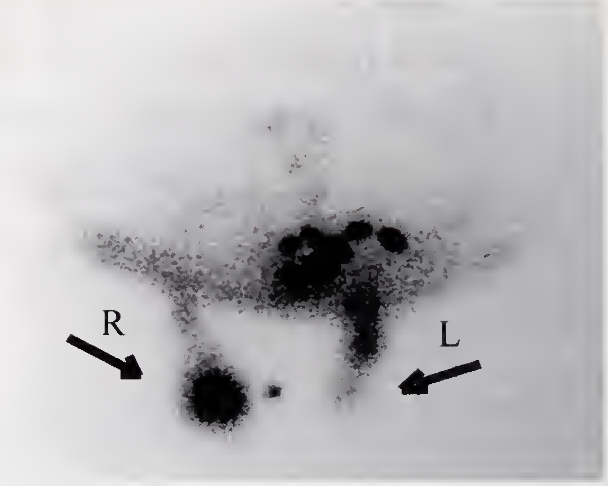

Fig. 2. Two hours post-instillation of radioisotope containing peritoneal dialysis fluid, the fluid has been removed from the abdomen. With the patient erect, radioactivity is clearly seen in the inguinal canals and right hemiscrotum (arrows) in the same view as in Fig. 1.

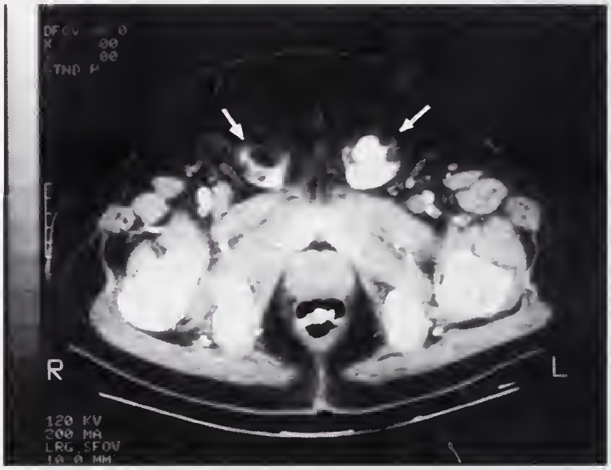

Fig. 3. CT scan shows contrast material, which has been added to the peritoneal dialysis fluid, in both inguinal canals (arrows).

CAPD was resumed four weeks after the herniorrhaphies. There was no recurrence of the patient's genital edema. After more than three years of follow-up, the patient is tolerating CAPD well; there has been no recurrence of the patient's genital edema or inguinal hernias.

Discussion

Peritoneal dialysis was first described by Ganter in 1923 (4). Tenckhoff and Schechter (5) reported the use of the first permanent indwelling peritoneal dialysis catheter in 1968. Popovich et al. (6) are given credit for developing the concept of continuous ambulatory peritoneal dialysis. This technique has evolved into a safe, practical and effective method of treating renal insufficiency.

The most commonly reported complication of CAPD is peritonitis. Other complications include mechanical flow obstruction, catheter migration, leakage at the catheter exit site, bowel obstruction, and perforation (2). Abdominal wall and inguinal hernias develop because high intra-abdominal pressures are present while the dialysis fluid dwells within the peritoneal cavity. This same high pressure can cause movement of dialysate through living membranes such as the peritoneum (7). Genital edema was first reported as a complication of CAPD by Khanna et al. (8) in 1981. In a retrospective study of 450 of their CAPD patients, Abraham et al. (9) found the incidence of this complication to be 4%; Kopecky and his associates (3) reported a 10% incidence in 81 patients.

There are two distinct mechanisms that can cause genital edema. In the first, a leak at the insertion site of the peritoneal dialysis catheter in the abdominal wall or other area of disruption of the peritoneo-fascial barrier allows extravasation of hypertonic peritoneal dialysate into the abdominal wall tissues. This fluid settles in the dependent genitalia. In the second mechanism, the increase in the intra-abdominal hydrostatic pressure, produced by the dwelling dialysate, causes translocation of this fluid through the peritoneal membrane that makes up an inguinal hernia or patent processus vaginalis (persistent sac) into the surrounding tissues. The incidence of indirect inguinal hernia is between 10 and 25% (7). A postmortem study of adults who died without clinically apparent inguinal hernias found a patent processus vaginalis (persistent sac) in 20% (10).

The etiologic mechanism that caused the genital edema is often impossible to detect by physical examination. This fact is, unfortunately, clearly illustrated in our case. The penile edema and absence of a palpable inguinal hernia, with which our patient presented, suggested to us that there was a leak of dialysate into the anterior abdominal wall. We took the patient to the operating room and instilled radiographic contrast into the peritoneal cavity. We hoped that fluoroscopic examination at that time would reveal the defect. In fact, no leakage along the catheter tract at the peritoneofascial insertion site or into a hernia was demonstrated. We elected to remove the peritoneal dialysis catheter and place a new one at a new site.

When the patient developed genital edema immediately upon resuming CAPD four weeks after placement of the new catheter, we performed two helpful diagnostic tests. Peritoneoscintigraphy was performed first. Gamma camera scanning identified radioactivity in the scrotum on both sides. Following this, the patient underwent CT scan as described above. This study, too, identified contrast material in both hemiscrota; no viscera were seen in the canals. The findings in both studies were consistent with bilateral patent processus vaginalae.

The patient later underwent bilateral inguinal hernia repairs with high ligation of the patent processus vaginalae. He has done well on CAPD without recurrence of genital edema over the past two years.

This case confirmed to us the necessity of performing at least one of these two diagnostic studies when encountering the CAPD patient with genital edema. Although our case illustrates the effectiveness of these studies in the patient with a patent processus vaginalis, others have reported similar success in the patient with anterior abdominal wall leaks (11, 12). These investigators have suggested that CT peritoneography is superior to peritoneoscintigraphy in the diagnosis of abdominal wall leaks because of its better anatomic resolution. Maxwell et al. (12) suggest repeating the scan at 4 and up to 24 hours after instillation of the contrast material in negative or equivocal cases when abdominal wall or genital edema is present.

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Mortality Associated with Concurrent Strongyloidosis and Cytomegalovirus Infection in a Patient on Steroid Therapy

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Abstract

Disseminated strongyloidosis has been recognized with increasing frequency, often in patients who are immunocompromised or have received steroid therapy. In addition, disease due to cytomegalovirus (CMV) is noted in immunodeficient hosts. We report on a 55-year-old Puerto Rican man who received steroid treatment for oropharyngeal pemphigus vulgaris and developed abdominal symptoms with alternating constipation and diarrhea. The clinical work-up did not reveal specific abnormalities, but the patient died of cardiopulmonary failure. At the postmortem examination, the patient had evidence of strongyloidosis and CMV disease. This report reviews both this case and the literature, and discusses the overlapping infections of strongyloidosis and CMV disease in this patient who had received steroid therapy. **Key Words:** Disseminated strongyloidosis, autoinfection, cytomegalovirus, steroid therapy, cardiopulmonary failure.

Introduction

Strongyloidosis is relatively uncommon in the United States but widespread in other regions. The infection is sporadic in the southern United States and Puerto Rico. Infected patients can present with rash and various pulmonary and abdominal complaints. Parasite dissemination associated with gram-negative bacterial sepsis has been reported in immunocompromised hosts (1–5). Hyperinfection due to *Strongyloides* depends on host immunity. And host immunity can be altered by iatrogenic modalities or natural diseases such as malignancies, acquired immunodeficiency syndrome (AIDS) or other medical conditions that may require corticosteroid therapy, chemotherapy and radiation, as well as organ transplantation (2, 6–10).

The infectious form of *Strongyloides stercoralis* is the long and slender filariform larva which develops in soil (11). Infection takes place by larval penetration through the skin. The larvae are then transported by the venous circulation through the right heart to the lung, where they enter the alveoli and then migrate up to the glottis and are swallowed. The final destination is the duodenum and proximal jejunum. Following a brief cycle, the female lays eggs within the intestinal mucosa. When hatched, rhabditiform larvae enter the bowel lumen and are expelled via the feces. These develop into free-living male and female worms which eventually produce infectious filariform larvae, to repeat the process. However, this parasite can also reproduce asexually. In this situation, rhabditiform larvae in the intestine develop into filariform larvae that penetrate the bowel and gain access to the circulation to repeat the infectious cycle. This autoinfection is a unique process of *S. stercoralis* that permits reappearance of the disease for decades after departure from endemic areas (2, 5, 12–14). A

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substantial number of patients are asymptomatic, but overwhelming infection may occur especially in patients immunosuppressed by diseases or therapy. When it occurs, this autoinfective cycle may occasionally become fatal, since the larvae are frequently accompanied by intestinal microorganisms that initiate sepsis in all loci visited by the larvae. While the hyperinfection state is characterized by severe gastrointestinal and respiratory tract involvement along with skin rash and/or bacteremia, it is curable when diagnosed and treated promptly (1, 6, 15). When disseminated strongyloidosis occurs in patients who complain of nonspecific abdominal pain, nausea, vomiting, diarrhea and weight loss, often following steroid therapy for unrelated conditions, mortality is high, around 80% (2, 6).

Cytomegalovirus (CMV) is a DNA virus, infecting 70–90% of the population without overt disease manifestation. Serious disease is reported in neonate and immunocompromised hosts. Asymptomatic, reactivated CMV infections are commonly associated with human immunodeficiency virus (HIV) infection. Serious end-organ CMV disease (e.g., retinitis, colitis and encephalitis) is considerably less frequent (16–18). This is a report about a case of fatal disseminated strongyloidosis in a Hispanic male who lived in New York City for the past 30 years. Postmortem examination revealed disseminated strongyloidosis concurrent with CMV disease. These two etiologic agents have not been described as occurring together even in patients on various steroid regimens.

Case Report

A 55-year-old Hispanic man was admitted to the Elmhurst Medical Center, Elmhurst, Queens, NY, complaining of abdominal pain for 3 weeks. The patient had been well until 5 months prior to admission, when he developed painful ulcers of the buccal mucosa and gingiva. Biopsies of those ulcers were diagnostic for pemphigus vulgaris. At that time, treatment with a daily dose of 60 mg of prednisone was begun. Two months prior to admission, the lesions had nearly resolved and a tapering dose of prednisone was instituted. Then, 3 weeks prior to admission, sharp and diffuse abdominal pain developed, with alternating diarrhea and constipation, not related to meals, and unresponsive to over-the-counter histamine (H_2) blockers. The patient became anorexic and lost about 30 pounds.

Historically, the patient was a native of Puerto Rico, residing in New York City for the past 30 years; he had visited Puerto Rico 5 years earlier. He had no history of fever, nausea, vomiting, skin rash or coughing, and denied use of tobacco or alcohol, or medication noncompliance.

On physical examination, the patient was moderately obese. His temperature was 38° C, pulse rate 80/min, and blood pressure 130/70 mmHg without orthostatic changes. There were no oral lesions. Abdominal exam was notable for diffuse tenderness on deep palpation. There was neither distention nor hepatosplenomegaly. On rectal exam, there was occult blood positive brown stool. Skin examination was normal.

The values for aspartic acid aminotransferase, alkaline phosphatase, bilirubin, amylase, and magnesium were within normal limits. The prothrombin and partial thromboplastin times were normal. The chest X-ray was also normal. The flat and upright abdominal X-rays demonstrated a large amount of stool.

The patient received normal saline infusion at 50 mL/hr, followed by furosemide intravenously. The use of oral fluid was restricted and the patient was started on intravenous solu-cortef 100 mg every 8 hours. Ciprofloxacin was administered intramuscularly.

Laboratory values obtained on the day following admission revealed serum osmolality 260 mOsm/L, urine osmolality 780 mOsm/L, urine sodium 48 mEq/L, urine potassium 46 mEq/L, and urine chloride 54 mEq/L.

There was some improvement in the abdominal pain. On the third hospital day, the serum sodium measured 128 mMol/L and fluid restrictions were discontinued. Blood cultures were negative and the morning serum cortisol measured 31 μg/dL.

On the fifth hospital day, the patient developed increasing abdominal pain accompanied by nausea and vomiting. The vomitus was brown and feculent, and had a coffee-ground appearance. The blood pressure dropped to 90/60 mmHg. The abdominal X-ray showed dilated loops of small bowel. At this point, the patient went into cardiopulmonary arrest and expired.

A postmortem examination was performed.

Results

Autopsy examination revealed heavily congested and consolidated lungs weighing 2 kg. The small intestine showed mucosal hyperemia, and the cecum was dilated with areas of ulceration. The colonic mucosa was hyperemic with multiple, large, irregular ulcerations. Some of these ulcers appeared hemorrhagic and linear, particularly in the areas of sigmoid, along with several diverticula. Microscopic sections of the lungs showed diffuse alveolar change with features of adult respiratory distress syndrome (ARDS). In addition, the right lung showed acute pneumonia (postmortem culture grew *Klebsiella pneumoniae*). An unexpected, striking finding was the presence of disseminated strongyloidosis involving multiple organs: lungs (Fig. 1A), large intestines (Fig. 1C), and mesenteric lymph nodes (Fig. 1D). Other organs involved were the heart, liver, pancreas, esophagus, and small intestines, as well as skeletal muscle. In addition, many CMV inclusions were identified in the lungs (Fig. 1B) and throughout the gastrointestinal tract.

The 2 liters of peritoneal fluid did not yield any larvae.

Discussion

Most of the mainland U.S. patients in whom *S. stercoralis* has been diagnosed originally came from the Caribbean region (4, 5, 12 – 14). Over the past 2 decades, cases of unsuspected strongyloidosis following corticosteroid therapy have become more frequent (19 – 22); when overwhelming infection with *S. stercoralis* accompanies unrelated conditions that are treated with corticosteroids, this treatment leads to the activation of dormant parasites and autoinfection. Reasonable caution should be exercised when patients who have resided for prolonged periods in areas endemic for the parasites receive therapy that leads to immunosuppression. Clinically, overt CMV disease also results from the depression of immunocompetence. Nevertheless, the concurrent emergence of strongyloidosis and CMV has not been described, in the immunosuppressed population at risk.

The diagnosis of strongyloidosis can be made quickly and noninvasively if clinically suspected (2). Laboratory examinations of at least 3 consecutive stool specimens, using direct and concentration methods, should be performed. A reliable and inexpensive serological test (ELISA) is available to detect anti-*Strongyloides* antibodies (23 – 26). In systemic strongyloidosis, routinely stained Papanicolaou smears of sputum can reveal the filariform larvae of *S. stercoralis* (10, 27). Duodenal aspirates, sometimes obtained with a string-test capsule, can lead to detection of rhabditiform larvae of *S. stercoralis*. Various culture methods may also be used (24).

Patients may present with vague abdominal symptoms such as anorexia, nausea, vomiting, and bloating and cramping with alternating constipation/diarrhea, attributable to various etiologies, but the diagnosis of strongyloidosis is made most often at necropsy, as in this case. This diagnosis may be missed primarily for lack of clinical suspicion, especially with patients from endemic areas (2, 21).

The respiratory symptoms in strongyloidosis are caused by the migrating larvae producing alveolar hemorrhage, edema and inflammatory changes. Adult worms are known to cause chronic bronchitis or asthma-like symptoms (19). Very often, the larvae carry intestinal microorganisms that further complicate the pulmonary lesions caused by the parasites. Enteropathy due to direct mucosal damage, impairment of intestinal lymphatic function and overwhelming presence of worms may impair absorption (2, 14, 20); involvement of liver results in elevated alkaline phosphatase and bilirubin (28).

Risk factors for systemic strongyloidosis include leukemia, lymphoma, chronic infection, transplantation and immunosuppressive therapy (6, 20, 21, 29, 30). Eosinophilia, if present, is an alarming clue. However, eosinophil counts tend to be lower in systemic infection and with the hyperinfection syndrome after corticosteroid therapy (2, 14, 25).

Prevention of disseminated strongyloidosis can be achieved in patients when an early diagnosis is made and prompt medical intervention is applied. Successful treatment in cases of disseminated strongyloidosis is achieved with conventional drugs like thiabendazole and mebendazole (31), but mortality in disseminated strongyloidosis remains at about 80% (1). Death is frequently the result of either secondary bacterial infections or respiratory failure.

In retrospective autopsy series, CMV inclusions have been observed in the lungs of more than 90% of AIDS patients. Both strongyloidosis and CMV are considered to be opportunistic infections in these patients (7, 8, 17, 32). However, the relationship between strongyloidosis and CMV is unknown; the coexistence of CMV with other opportunistic pathogens has not been fully elucidated. In Jacobson's experience (16), CMV pneumonitis is almost always an incidental diagnosis after bronchoscopy performed on patients with symptomatic interstitial lung disease. The isolated presence of CMV in bronchoscopy specimens may or may not be associated with progressive clinical pneumonitis (16). CMV infections of the GI tract include colitis, esophagitis and gastritis. Successful use of ganciclovir to prevent and treat CMV infection has been widely accepted. Foscarnet, another antivi-

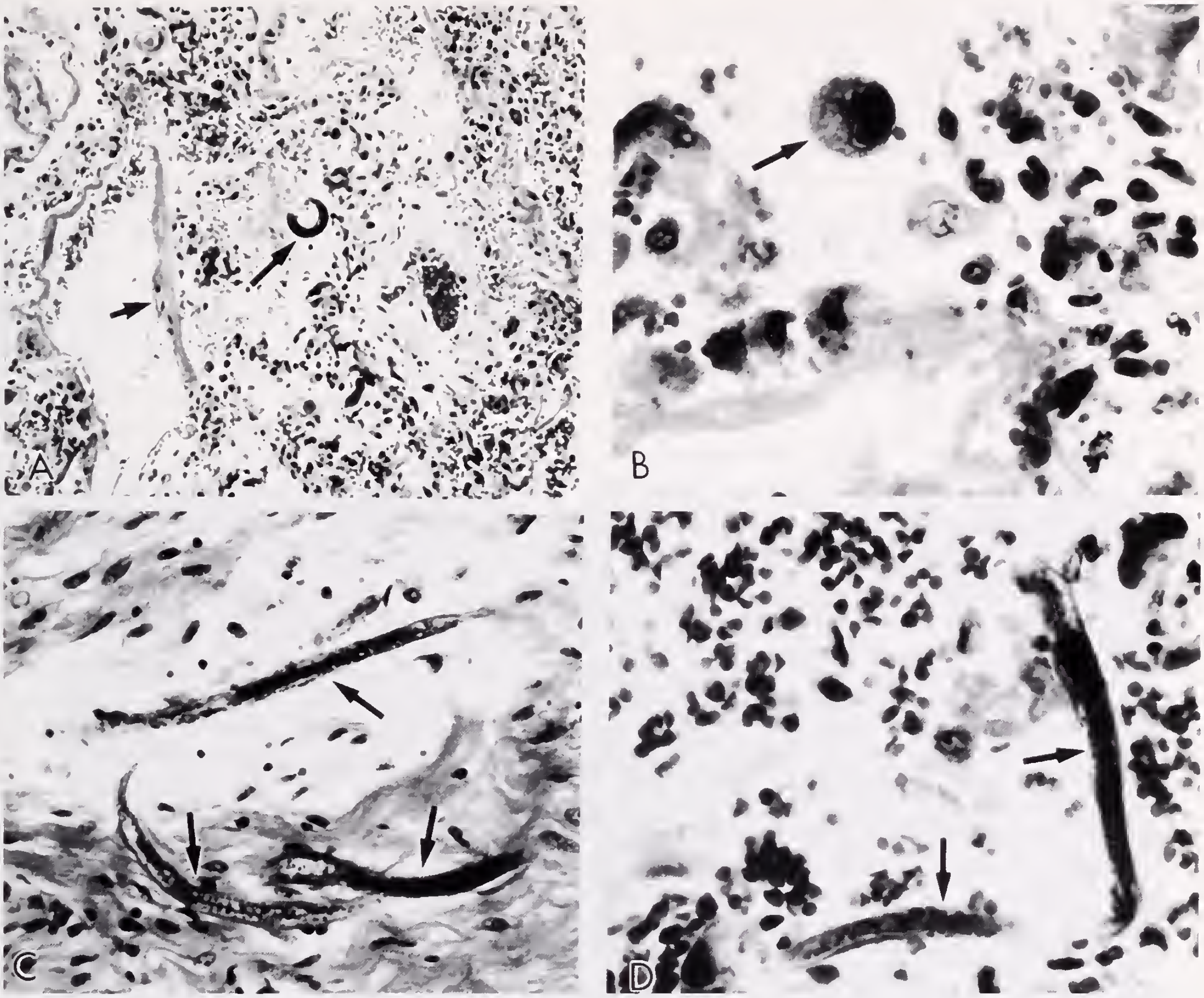

Fig. 1. A. Section of the lung showing extensive acute pneumonia with diffuse alveolar changes of ARDS. A rhabditiform larva of *Strongyloides* migrating through the lung parenchyma (arrow), adjacent alveolar space lined by hyaline membrane (arrowhead) (H-E, x200). B. High magnification of lung section showing a large cell containing a classic CMV inclusion with background of acute pneumonia (arrow) (H-E, x800). C. Section of large intestinal wall showing three larvae (arrows) (H-E, x400). D. Section of mesenteric lymph node showing two larvae (arrows) (H-E, x400).

ral agent, may also be used in the treatment of CMV infection, often in combination with ganciclovir for immunosuppressed patients, or with zalcitabine for therapy of AIDS patients (33–35).

The possibility that CMV or other viruses may be carried by the migrating larvae is an intriguing factor, despite our inability to support this view in this HIV-negative patient, who had resumed steroids for an unrelated condition (3, 16, 17, 22). This case illustrates the need to consider carefully the combination of therapeutic regimens to be used in those patients at risk, even though the clinical manifestations are subtle. To the best of our knowledge, this report represents the first case in which both *S. stercoralis* and CMV were found. This suggests that some viruses may join enteric bacteria as companions of migrating larvae (18, 20, 21).

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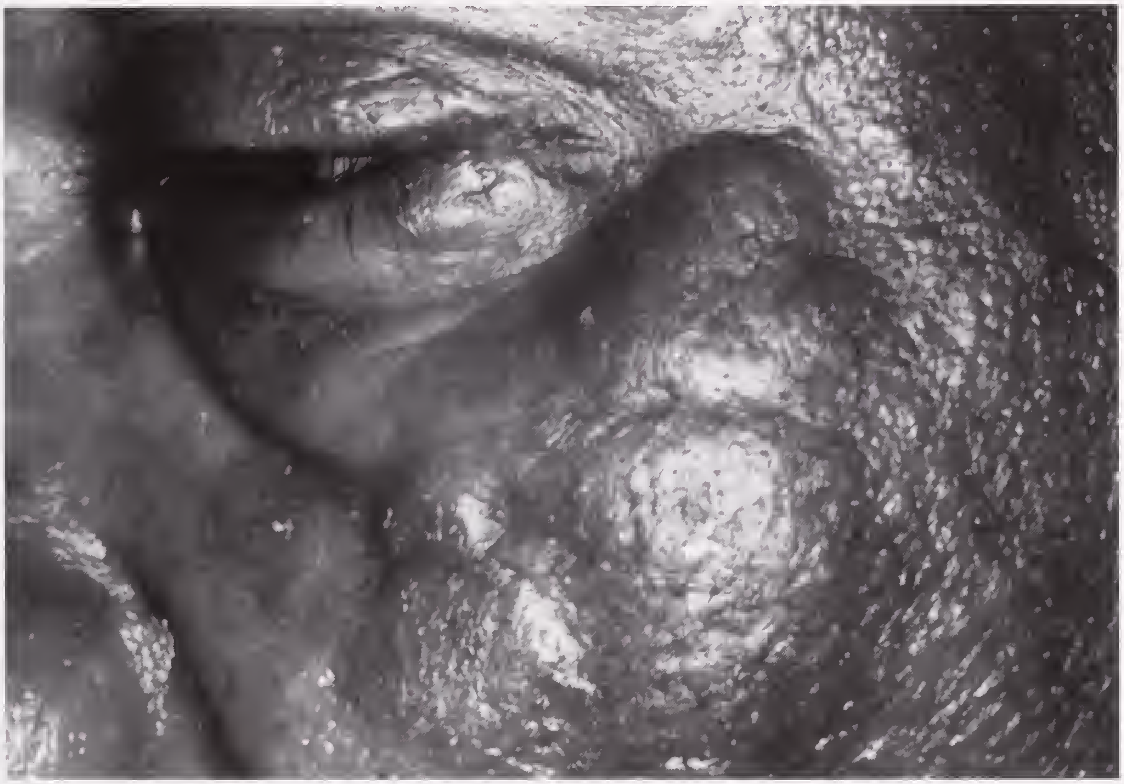
Actinic Reticuloid



PATIENTS WITH THIS DEBILITATING DISEASE are exquisitely sensitive to light. They are often unable to tolerate sunlight or fluorescent lights and must live in dark rooms.

—Marsha Gordon, M.D. and Mark Lebwohl, M.D.

Book Review

Understanding Acid-Base

Benjamin Abelow, M.D. Baltimore, Philadelphia, London, Paris, Bangkok, Buenos Aires, Hong Kong, Munich, Sydney, Tokyo, Wroclaw: Williams & Wilkins; 1998. 333 pp, index and appendix. $24.95. ISBN 0-0683-18272-2

TEACHING THE FUNDAMENTALS OF ACID-BASE is not an inconsequential component of medical education, and mastering concepts is not a trivial exercise. Yet, for the most part, the essentials of this crucial subject are fragmented within Biochemistry and Physiology, as well as in Pediatrics, Medicine, Intensive Care and various clinical subspecialties where the student, house officer, practitioner and specialist will be challenged by actual patients in whom an acid-base derangement represents a major, if not, life-threatening disorder. Dr. Abelow, Lecturer in Medicine at Yale University School of Medicine, has undertaken to integrate the many segments to facilitate a clearer understanding of the core aspects by the reader-student.

The book is divided into an introductory review of the fundamentals and five sections entitled Chemistry, Physiology, Pathophysiology, Diagnosis, and Treatment, each of which is further subdivided into brief chapters. An appendix addressing, in brief, twelve topics of special interest is intended to move the reader "one level deeper." An annotated bibliography and an index conclude the book.

The book is well written and achieves its stated objective of making the subject of acid-base readily understandable to a very broad audience. The author clearly states, at the very beginning of the first chapter entitled "Review of Fundamentals," that this section is directed toward first year medical students. Many readers might find this introduction to the elementary concepts overly simplistic and, as the author suggests, might elect not to spend any time on it except as a refresher. This option might be taken by many with respect to the material on buffers through to the discussion of bicarbonate as a buffer system. The author's intent in including this material is to assure that all readers have been suitably prepared to address the information and to digest the concepts to be presented subsequently. A notable and worthy approach is the inclusion of a self-assessment quiz at the end of this section. The reader's performance in answering the questions should be decisive with respect to investing the time, or not, to read the introductory material. I might add that each subsequent section has its own well-thought-out and constructed self-assessment quiz which I found to be a useful evaluation of how well the material has been presented by the author and grasped by the reader.

The second section is devoted to various aspects of acid-base physiology such as regulation of arterial PCO_2, renal bicarbonate reabsorption and regeneration, and acid production and excretion. All of these topics are of crucial importance and are handled by the author with style and dispatch. Clearly, the text is devoted to how two major organs, the lungs and kidneys, modulate acid-base regulation. In the case of the lungs, the basic concepts of alveolar ventilation and diffusion are presented succinctly to assure that the reader has no doubt about how the partial pressure of CO_2 (PCO_2) is regulated. With respect to the kidneys, a brief review of the nephron sets the stage for a well-illustrated discussion of hydrogen ion secretion and bicarbonate reabsorption which occur in the various segments of the nephron. There is also a brief mention of the "proton pump" in the distal tubule. Following this material, the text turns to a discussion of acidification of body fluids. Most textbooks addressing the subject of acid-base do not provide much insight into the inseparable relationship between energy and acid-base metabolism. This is not to say that a full exposition of the subject should be provided in texts dealing with acid-base, but surely some details would help the reader realize that any gaps in his or her knowledge base with respect to the relationships between tissue oxygen consumption and CO_2 production, and aerobic and anaerobic ATP synthesis and proton production, must be closed. Integrating this component directly into the text would be well worth the effort by the author, who has been so successful in handling all of the other material. I am sure that the reader would come to value and appreciate Dr. Abelow's insight and style in presenting this material as well. What the author has done, however, is to exemplify, graphically and in narrative form, how the outcomes of metabolizing several different kinds of substrates impact on acid-base. The reader will find this discussion to be easily comprehensible. Continuing this approach, the text goes on to briefly mention the consequences of anaerobic metabolism of glucose to lactic acid, and the incomplete oxidation of triglycerides. A short discussion of protein metabolism highlights the different roles played by various amino acids in acid-base balance. A brief discussion, but a most useful and very essential one, describes the contributions of the various parts of the GI tract to the acid-base story. Herein, the author captures the essence of how the different segments work and how they are distinctly different.

Within this section on Physiology, there are two brief chapters and a concluding overview which deal, first, with acid excretion or bicarbonate regeneration, and then an integrated view of renal bicarbonate handling. Again, the text is amply illustrated with several easy to understand figures.

The third section is entitled "Pathophysiology." Here lies the essence of what has gone on before. The reader is introduced to the language and precise meaning of each of the terms generally used in describing the clinical status of patients with acid-base disorders. The brevity of the presentation does not short-change the reader, and may even represent a strength. The text addresses the three main body compartments involved in buffering and their relative importance. Mechanisms of compensation are clearly illustrated. However, I am concerned with the explanation offered with respect to the compensatory sequences for metabolic derangements of acid-base, in that only a passing mention is made of the existence of the blood-brain barrier. The respiratory center, functioning as a central chemoreceptor, is certainly responsive to PCO_2, H^+ and HCO_3^- but the blood-brain barrier plays an important role in determining the composition of the cerebrospinal fluid and the brain's interstitial fluid, which differ uniquely from the extracellular and interstitial fluids of other organs and tissues. This information is so fundamental that the author's footnote is hardly adequate. But the subsequent discussion of metabolic acidosis and alkalosis is as illuminating as it is concise. The same can be said of the presentations on respiratory acidosis and alkalosis. The reader will welcome these presentation of the concepts as well as specific factual information. However, I was unable to find any mention of alveolar capillary block. Despite a section entitled "The work of breathing," the reader is not exposed to a definition of "work," how it is measured, and the clinical consequences when more of it is required in the several conditions elaborated upon by the author. The function and role of the elastic tissue in the lung are not mentioned, although the reader is informed, and correctly so, about the highly elastic lung being stiff and non-compliant. But the book is not intended as an exposition of pulmonary physiology. The mention of the blood gas composition of a mountaineer at the top of Mount Everest is titillating and it would have been helpful if the appropriate reference had been provided for those inquisitive enough to explore human adaptability to such extreme conditions.

The fourth section is devoted to "Diagnosis" and is divided into five chapters. The initial section deals with the need for the clinician to have a high index of suspicion of the acid-base derangement just from the history and physical examination as a basis for ordering the appropriate laboratory tests. A number of conditions are enumerated which are potential causes of acid-base disturbances. The utility of knowing the concentrations of electrolytes in venous blood, and the gases in arterial blood, is thoughtfully detailed along with nomograms. Similarly, some additional tests and their limitations are also enumerated. The reader is challenged to integrate these data into a knowledge base which can be recalled, but if this appears insurmountable, the author suggests that the reader may want to photocopy, for ready reference, a nicely laid out one-page table entitled "Typical Laboratory Presentations of Common Acid-Base Disturbances."

The final section of the book is devoted to "Treatment." The author does provide numerous details which are beyond the scope of this review. In some instances, the reader might have wished more specifics regarding, for example, the suggested rate of intravenous administration of potassium when indicated, as well as other modalities.

The final part of the book is an "Appendix" which consists of topics A-L. Herein, the author provides the reader with more information on renal ammonium handling, anion gap, osmolar gap, and renal tubular acidosis amongst others. The final topic is a description, and in many ways an endorsement, of the use of local or topical anesthesia prior to arteriopuncture. The author does not address the use of capillary blood from a finger stick to determine blood gas concentrations, or the use of an "arterialized" venous sample obtained by immersing an arm in a water bath at 40°C for five minutes or so. Either approach could avoid the risk and discomfort of an arterial puncture, even with a fine needle.

In summary, I think the author has achieved the stated objectives he set out to accomplish. I can recommend the book to medical students and house officers who want to broaden their horizons with a firmer grasp of the road map, with its many highways and byways, into acid-base and surrounding territories.

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THE
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Correction

We regret errors in an abstract printed on p. 71 of vol. 66, no. 1, January 1999. The authors should have been listed in the following order: C. Patel, A. Husain, E. Restrepo, and F. Rosner. Also, it should be noted that the patient was hospitalized because of a "2-month history," not a "2-year history" of pain and fever.

ANNOUNCEMENT OF 1998 AWARDS

The Mount Sinai Journal of Medicine offers several prizes for manuscripts published in *The Journal* during the previous year and judged by an Awards Committee to be outstanding contributions to the medical literature. The committee's task certainly was formidable, but I believe that it has chosen wisely and well. The efforts of the members are much appreciated.

The 1998 Globus Award, established in honor of the first and long-time editor of *The Journal,* is for the best overall paper on a clinical topic. The award goes to Mitchell H. Grayson, M.D., and Bruce S. Bochner, M.D., for their paper entitled "New Concepts in the Pathogenesis and Treatment of Allergic Asthma," Volume 65, No. 4, pp. 246–256.

The 1998 Ralph Colp Award, in honor of the memory of a distinguished Chief of Surgery at The Mount Sinai Hospital, for the best paper on a surgical topic goes to Pamela L. Alberto, D.M.D., for her paper entitled "Implant Reconstruction of the Jaws and Craniofacial Skeleton," Volume 65, No. 5, pp. 316–321.

On behalf of the Editorial Staff, I am delighted to recognize the outstanding scholarship and contributions of our 1998 awardees to medicine in general, and to *The Mount Sinai Journal of Medicine* in particular.

Sherman Kupfer, M.D.
Professor of Medicine,
Physiology and Biophysics
Editor-in-Chief

Introduction

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PHYSICAL MEDICINE AND REHABILITATION (PM&R) is a wide-ranging and multifaceted specialty. However, quoting Dr. Edward Lowman, (1), "Its focus...is the patient, and its effectiveness is in direct proportion to one's skill in recognizing and dynamically meeting the total needs of [one's] patient despite the residual disability and its implications...." (1)

The PM&R specialist (physiatrist) encounters patients with diverse diagnoses (e.g., traumatic brain injury [TBI], spinal cord injury [SCI], stroke, arthritis, cardiovascular disease, congenital disorders, etc.). Frequent interaction between the physiatrist and other medical and surgical specialists is therefore required. In addition, the resulting disabilities (e.g., hemiplegia, paraplegia, tetraplegia, ataxia, back pain, deconditioning, limb loss, etc.) require the physiatrist to coordinate the efforts of an interdisciplinary team. This team may include physical therapists, occupational therapists, nurses, social workers, psychologists, speech pathologists, vocational counselors, and recreational therapists, among others.

In this first-ever theme issue of *The Mount Sinai Journal of Medicine* focusing on rehabilitation medicine, Dr. Kristjan Ragnarsson (Fig.), who assumed the chairmanship of the department in July 1986, traces the history of this specialty at the Mount Sinai Medical Center. He also addresses the future of the specialty in the changing health care environment.

Fig. Dr. Kristjan Ragnarsson.

Rehabilitation medicine helps people after devastating injuries. Drs. Dyson-Hudson and Stein explore the acute management of people who have sustained traumatic cervical SCI. Dr. Spungen and her colleagues at the Bronx Veterans Affairs Medical Center examine how a medication may improve breathing in people with this disability.

PM&R is also concerned with people who sustain less obvious injuries. Dr. Flanagan discusses mild TBI, and emphasizes the need for a high

Issues in Rehabilitation Medicine

index of suspicion for symptoms of this disorder.

As longevity has increased, so has the need for delivery of primary health care services for people with disabilities. Dr. Thomas explores this problem in his article.

Rehabilitation medicine has much to offer the general population as it ages. In my article, I examine the commonalities between PM&R and geriatrics, as both fields work to improve the prevention and treatment of illness and disability in the elderly.

Osteoporosis is a widespread bone disorder that has received increased attention in recent years. Dr. Sheth addresses the role of exercise in the management of this condition.

Dr. Nainzadeh and her colleagues explore the role of rehabilitation medicine in the management of repetitive strain injury, in view of the increasing incidence of this condition in the home and the workplace.

Since its inception, PM&R has been concerned with improving quality of life (QOL). However, defining and measuring QOL have been problematic, as Drs. Brown and Gordon demonstrate in their article.

A major contribution to an improved QOL is increased function. Dr. Eastwood describes how monitoring organizations and regulatory agencies are using diverse data collection systems (e.g., the Functional Independence Measure [FIM]) to document functional changes.

Increasing research, improving education, and developing more creative means of service delivery are the keys to progress in PM&R (and many other fields). This issue of *The Mount Sinai Journal of Medicine* addresses some of these efforts by our Department of Rehabilitation Medicine. The value of these contributions, however, will best be judged in the next century.

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Physical Medicine and Rehabilitation at the Mount Sinai Medical Center During the 20th Century

Kristjan T. Ragnarsson, M.D.

Abstract

The Department of Rehabilitation Medicine at the Mount Sinai Medical Center has a long history, beginning in 1910 with the establishment of the Department of Physical Therapy, headed by Heinrich Wolf, M.D. In 1935, William Bierman, M.D., was appointed director. He was, at that time, one of the leading physicians of physical therapy in the United States, and a prolific researcher, writer and clinician. In 1948, the name of the department was changed to the Department of Physical Medicine, reflecting the newly established specialty of the Board of Physical Medicine. In 1959, Lawrence Wisham, M.D., was appointed chairman, and shortly thereafter the name of the department was changed to Physical Medicine and Rehabilitation. Under Dr. Wisham's leadership, services were provided to inpatients on the acute wards of the hospital, and to outpatients. In 1968, the name of the department was changed to Rehabilitation Medicine. In 1986, Kristjan T. Ragnarsson, M.D., became chairman of the department, and shortly thereafter an inpatient rehabilitation medicine service was established and outpatient services expanded. Since that time, rapid growth has occurred within the department, particularly in delivery of clinical services and research. The role of rehabilitation medicine in the delivery of clinical services to people with temporary or permanent disability is now well established, but efficient and effective delivery must be ensured in the current and future healthcare environment. **Key Words:** Physical therapy, physical medicine, rehabilitation medicine, history.

The great medical authors of ancient times, including Hippocrates and Galen, mention in their writings the use of physical agents to treat disease and to improve health and human function. Physical agents such as, heat, cold, water, sun rays, exercise and massage have been widely used on an empirical basis throughout the ages, with electricity being added more recently. In the early twentieth century, Marie Curie received the Nobel Prize for Physics for her work on radioactivity (1903) and the Nobel Prize for Chemistry for her discovery of radium and polonium (1911). Niels Finsen, M.D., an Icelandic physician practicing in Denmark, received the Nobel Prize for Medicine in 1903 for his work on the effects of ultraviolet rays on animal organisms. Unfortunately, few scientific studies were done on other physical agents, so that the use of many agents gradually fell out of favor by the medical profession, and often was regarded as a form of quackery.

1910–1935

It was in this atmosphere that the Department of Physical Therapy of the Mount Sinai Hospital Dispensary was established on December 5, 1910, as an independent unit with representation on the Medical Board by its chief, Heinrich Wolf, M.D. Prior to this time the physical therapy services had been "under the supervision of the orthopaedic division" (1). According to a report written by Dr. Wolf in 1912 (2), the treatment provided by the medical staff of the department consisted mostly of applying hot air and performing massage for such medical conditions as bone fractures, joint diseases and constipation (!), reportedly with good results. Dr. Wolf believed that The Mount Sinai Hospital was the first hospital to acquire a modern diathermy apparatus and one of the first to use artificial fever in the treatment of disease.

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1935–1959

There is little information available about activities within the department until 1935, when William Bierman, M.D. (Fig. 1), one of the pioneers of physical medicine as a specialty (3) was appointed attending physical therapist (and apparently director of the department). (In those days all physical therapists were physicians.) Dr. Bierman, together with two other founders of the specialty, Frank Krusen, M.D., and John Coulter, M.D., established the American Board of Registry for Physical Therapy Technicians in 1934, in order to evaluate and register therapists who were considered qualified (4). From 1932 to 1938, he served on the editorial board of the *Archives of Physical Therapy, X-ray and Radium*, the publication that became the *Archives of Physical Medicine* in 1945 and the *Archives of Physical Medicine and Rehabilitation* in 1953. In 1936, Dr. Bierman was elected President of the American Congress of Physical Therapy, now the American Congress of Rehabilitation Medicine. That same year, Dr. Bierman was one of the first to advocate establishing physical medicine as a specialty, to the AMA Advisory Council for Medical Specialties (now the American Board of Medical Specialties) (5). In 1937, Dr. Bierman organized the first international conference on fever therapy in New York City. For his contributions in this field, the French government awarded him the rank of Chevalier (Knight) of the Legion of Honor.

Fig. 1. William Bierman, M.D.

Under his leadership, the department expanded and opened an inpatient division which, in 1938, obtained new quarters with a well-equipped gymnasium for therapeutic exercises, hydrotherapy facilities, a wide range of devices for electromagnetic therapies, and three rooms with equipment for fever therapy. At the opening of this new facility, an all-day presentation of scientific papers by the Department of Physical Therapy and other "cooperating" departments was held on April 13, 1938, and many of these papers were subsequently published in the September/October issue of the *Journal of the Mount Sinai Hospital* (3). The articles describe the use of different physical agents in the management of diseases, such as ultraviolet light for skin infections, conversive heat and iontophoresis for osteoarthritis, and artificial pyrexia (fever therapy) for achalasia and gonococcal infections.

In 1938, Dr. Bierman helped found the Society of Physical Therapy Physicians, now known as the American Academy of Physical Medicine and Rehabilitation (4). He served as the third president of this organization from 1940–1941. In 1941, Dr. Bierman received the Gold Key Award, the highest honor given by the American Congress of Physical Therapy (the other recipients that year were President Franklin Delano Roosevelt and Bernard Baruch, the financier and philanthropist).

During his career, Dr. Bierman was the author of three books, many book chapters and more than 100 scientific articles. He reached the age of retirement in 1958, but spent the next 10 years at the University of California, San Francisco, where he did research in biomechanics. He died in 1973.

There is little material available to describe activities within the department during the 1940s. During this period, antibiotics became widely available, eliminating the need for fever therapy in the treatment of infectious disease. During World War II, the focus of physical medicine broadened to include rehabilitation of persons with physical disabilities. This development was partly due to the large number of wounded soldiers in military hospitals, but also due in part to the passing of new legislation aiding persons with physical disability. During the war, Howard A. Rusk, M.D., introduced into Army Air Corps hospitals the concept of active rehabilitation of injured soldiers, emphasizing physical training as well as psychosocial counseling. In 1943, the Barden-LaFollette Amendment, commonly known as Public Law 113, was passed by Congress to permit availability of funds for physical restoration, in addition to vocational training, for persons with physical disabilities. After the war, Dr. Rusk and his colleagues initiated rehabilitation programs for civilians with physical disabilities and began efforts to establish rehabilitation medicine as a new medical specialty with approved residencies.

In June 1947, the American Board of Physical Medicine was established and approved by the Advisory Board of Medical Specialties (ABMS). That same year, 93 physicians were certified by the board, after passing oral and written examinations, and approximately 30 were certified without examination (6). Perhaps related to this development, the department changed its name from Physical Therapy to Physical Medicine on May 11, 1948. In 1950, the name of the board changed to Physical Medicine and Rehabilitation, as these two medical specialties merged into one. This merger was not approved by all; one of the most vocal opponents was a physician, Sidney Licht, who had trained and worked with Dr. Bierman at Mount Sinai (7). There is no indication that any comprehensive rehabilitation programs were established at Mount Sinai, either for inpatients or outpatients, during this period. Most of the treatments involved the use of physical agents, although there are numerous indications in the Mount Sinai Annual Reports that physical exercise and skills training for patients with physical disabilities were gradually becoming more important.

1959–1986

In January 1959, Lawrence A. Wisham, M.D. (Fig. 2), was appointed chairman of the Department of Physical Medicine. Shortly after his appointment, on March 10, 1959, the name of the department was changed to Physical Medicine and Rehabilitation (PM&R). Dr. Wisham is best known for his investigations on the clearance of sodium from human muscle, some of which he did in collaboration with Dr. Rosalyn Yalow, the Nobel Prize recipient for medicine and physiology in 1977. During Dr. Wisham's tenure, the department primarily provided consultation services to inpatients on the acute wards of the hospital and in various outpatient clinics, but did not have an active inpatient service. In the spring of 1964, the Rehabilitation Workshop, a project of the Women's Auxiliary Board, began providing paid employment in a sheltered environment for outpatients with disabilities—individuals who were unable to work in a competitive commercial environment but who hoped to gain employment in the future. On July 1, 1966, the department began a three-year training program in PM&R, with eight residents and fellows who had received a federal traineeship grant from the Vocational Rehabilitation Administration.

Fig. 2. Lawrence A. Wisham, M.D.

During the early 1980s, there were five physiatrists on the faculty at Mount Sinai. Besides Dr. Wisham, these were Drs. Frances Dworecka, Danuta Janiszewski, Somchat Chiamprasert and Beatrice Kaplan. A residency training program, for 24 residents, was directed by Jerry Weissman, M.D., at Elmhurst Hospital. These residents rotated through four hospitals: Elmhurst City Hospital, Beth Israel Medical Center, The Bronx Veterans Affairs Medical Center (VAMC) and The Mount Sinai Hospital. There were no federally funded research programs within the department, nor have I been able to find any history of such.

On the national scene, during the 1950s and 1960s, a small number of academic medical centers established their own departments of PM&R, which incorporated inpatient hospital beds for the rehabilitation of persons with severe physical disabilities. Teams of rehabilitation professionals were created, consisting of specialists in PM&R (physiatrists), physical, occupational and speech therapists, as well as rehabilitation nurses, psychologists, social workers, vocational counselors, recreational therapists, etc. These people worked together under the direction of the physician to reach the goals of rehabilitation medicine. The goals were defined as maximizing the function of the disabled person physically, psychologically, socially and vocationally. In 1965, the U.S. Congress passed legislation creating Medicare and Medicaid, and through diligent advocacy of leaders in the field of PM&R, rehabilitation services for both inpatients and outpatients were included in the Medicare/Medicaid health care package. Since that time, rehabilitation services have become a standard component of health care services in the United States for all persons with a new onset of physical disability. On May 20, 1968, the name of Mount Sinai's Department of Physical Medicine and Rehabilitation was changed to its current name: the Department of Rehabilitation Medicine.

Until the mid-1970s, inpatient length of stay (LOS) at rehabilitation institutions remained relatively long. At this time, many insurance companies became cost conscious and wanted to have an influence on the management of their patients. They demanded that rehabilitation centers establish criteria for patients to be admitted and criteria for continued stay; most rehabilitation services complied. During the early 1980s, as the flow of patients admitted for rehabilitation increased, there was also an increased demand for accountability. While the need for rehabilitation services for patients with physical disability was not an issue, the question was raised as to how the value of rehabilitation services could be measured, to justify its cost. It was generally agreed that the primary product of rehabilitation therapies was improved function. A variety of functional assessment scales were proposed, but many of these were found to be too complex to be practical, and others were found not to be scientifically valid or reliable. Finally, one functional assessment scale emerged, the Functional Independence Measure (FIM), which has been adopted by virtually all of the major rehabilitation centers in the U.S., These centers now collect functional data on admission, on discharge, and on follow-up for each patient.

During the 1980s, the U.S. Government established a new payment system for hospitals. Called the diagnosis-related groups (DRG) system, it prospectively assigns a specific number of inpatient days for each specific diagnosis. This payment system was created to give hospitals an incentive to reduce their LOS and consequently to reduce cost of care. Acute-care hospitals were paid a fixed price, depending on the specific diagnosis, regardless of whether the patient stayed less than the assigned number of days, or more. If hospitals were able to shorten the LOS for patients with acute illnesses, they were able to make more money than under the per diem payment system, but if the LOS was long, they would lose money. Two types of medical services were exempt from the DRG payment system: rehabilitation medicine and psychiatry. The DRG exemption proved to be very good for the field of PM&R. Since hospitals continued to be paid per diem for rehabilitation admissions, but not for admissions to the acute-care medical and surgical services, there was a financial incentive to open up more rehabilitation beds. Needing to shorten acute-care LOS, hospitals discharged patients earlier from the acute-care services and often transferred them to the inpatient rehabilitation medicine service. This resulted in a great increase in referrals of patients for inpatient rehabilitation, and increased the demands for rehabilitation beds. Since 1980, the total number of inpatient rehabilitation beds in the United States has more than doubled and is now well in excess of 22,000. Most of the new rehabilitation beds have been opened within hospitals; relatively few new free-standing rehabilitation centers have been built. This too has been advantageous for the field, since patients who arrive earlier for rehabilitation after illness or injury tend to be sicker and need continued access to hospital resources for proper management while they receive rehabilitation therapy. At the same time, more young physicians have been attracted to the field of PM&R, which now counts more than 5,000 specialists.

1986–Present

By the mid-1980s, it was clear that both The Mount Sinai Medical Center and its Department of Rehabilitation Medicine were about to undergo major changes. A new hospital building was being planned and a search committee was established to find a new chairman for the department. When Mount Sinai applied for a certificate of need (CON) for the new hospital building, to the New York State Commissioner of Health, David Axelrod, M.D., the CON was ultimately granted with the provision that there would be a reduction in the total number of beds in the hospital, but that 50 beds would be set aside for inpatient rehabilitation. After the search committee (led by Julius Wolf, M.D., Chief of Staff at the Bronx VAMC), had identified me as their leading candidate, a long process of negotiation regarding space and staff began. By July 1, 1986, when I assumed the chairmanship, Mount Sinai had made known its new commitment to provide comprehensive rehabilitation services for people with physical disabilities and to facilitate rehabilitation research and education. Since that time, remarkable growth has occurred in the various activities of the department, including expansion of inpatient and outpatient care services, educational programs and externally funded research. This has involved a large increase in the number of faculty and staff in the department. Some of the major highlights in the growth of the department will be described in the following paragraphs.

In December of 1986, eight inpatient rehabilitation beds were opened on the seventh floor of the old Housman Pavilion and the service grew to 17 beds in 1987. Joining me as an attending physician for this service was Joseph Carfi, M.D., a graduate of Mount Sinai School of Medicine, who completed his training in PM&R at the Rusk Institute. The inpatient service grew to 36 beds early in the year 1990, when it moved to the new Guggenheim Pavilion, and in 1992 it grew to 50 beds. In 1996, the inpatient rehabilitation service moved to renovated, state-of-the-art facilities on the second and third floors of the Klingenstein Care Center (KCC). Each inpatient unit of 25 beds was self-contained, with all rehabilitation services provided on the same floor as the nursing unit. One unit, directed by Adam Stein, M.D., is primarily for patients with spinal cord disorders, while the other unit, directed by Steven Flanagan, M.D., provides services for patients with disabilities caused by stroke and traumatic brain injury. In December of 1997, a third self-contained inpatient rehabilitation unit was added; it is located on the fifth floor of KCC. This unit, directed by David Thomas, M.D., is intended to provide services primarily for patients with physical disabilities of non-neurological causes.

Outpatient rehabilitation services have expanded both on and off the Mount Sinai campus. In 1986, outpatient rehabilitation services were provided only in the sub-basement level of 5 East 98th Street, the old Guggenheim Hall, but in 1996 the outpatient services moved completely to the current facilities in the new Guggenheim Pavilion, main corridor level. In 1992, the Mount Sinai Sports Therapy Center opened at 625 Madison Avenue; it is an elegantly designed outpatient physical and occupational therapy facility, fully equipped with state-of-the-art therapeutic devices and staffed by therapists experienced in the treatment of musculoskeletal disorders. In 1993, the department opened a new outpatient physical therapy facility at "Asphalt Green Swim and Sports Center," at East 92nd Street and York Avenue. Unfortunately, this facility was closed in 1996, when the landlord terminated the lease.

Electrodiagnostic services are provided by Nahid Nainzadeh, M.D., for both inpatients and outpatients. Richard Frieden, M.D., has developed rehabilitation services for persons with amputations and the geriatric population. Parag Sheth, M.D., working closely with Mount Sinai's Center for Corporate Health, has provided consultation services for persons with musculoskeletal disorders, as well as for sports- and work-related injuries.

There has been considerable interaction with hospitals within the Mount Sinai Health System, other than the traditional academic affiliates. One very significant development has been the close collaboration with Jersey City Medical Center and Meadowlands Hospital in New Jersey, in opening, staffing and operating the Liberty Rehabilitation Institute at Meadowlands Hospital. A 30-bed inpatient rehabilitation unit opened there in December of 1996. Jorge Mayoral, M.D., has been the unit's medical director since its inception. The department has also provided guidance and assistance to many other hospitals within the Mount Sinai Health System regarding establishment of new rehabilitation medicine services and recruitment of professional staff, including medical directors. In July of 1998, 26 representatives from 12 system hospitals with rehabilitation medicine services met for the first time at Mount Sinai to discuss future collaboration and networking.

At the same time as the clinical programs have grown, federally funded rehabilitation research projects have increased significantly. In 1986, the department was funded by the National Institutes of Health (NIH) for a research project on diagnosis and treatment of post-stroke depression. In 1987, the department was designated and funded by the National Institute of Disability and Rehabilitation Research (NIDRR) for five years as a traumatic brain injury (TBI) model system of care. In 1989, the Spinal Cord Damage Research Center at the Bronx VAMC opened under the direction of William A. Bauman, M.D., who holds joint appointments in the departments of Rehabilitation Medicine and Medicine. In 1990, the department received a designation and federal funding as a spinal cord injury model system of care, the only such system currently operating in New York State. In 1990, it received additional funding as a comprehensive regional TBI rehabilitation and prevention center. In 1993, the department was designated and funded as a research and training center to assimilate individuals with TBI into the community.

Working closely with Dr. Bauman on many of his projects is Ann Spungen, Ed.D. The center, which was established with funding from Mount Sinai and the Eastern Paralyzed Veterans Association, has been highly productive in terms of publications and presentations, and successful in obtaining grants from the Department of Veterans Affairs, NIH and non-federal agencies. Numerous other research grants have been obtained, both from federal and non-federal sources, with the annual funding for research (exclusive of Dr. Bauman's funded projects) varying between $1 million and $2.4 million annually. Instrumental in this success has been Wayne A. Gordon, Ph.D., a neuropsychologist, who began his career at New York University Medical Center, but joined me at Mount Sinai as director of research and associate director of the department in 1986. A close associate of Dr. Gordon's on most of his research projects is Mary Hibbard, Ph.D., who joined the department in 1986. As products of the research projects, numerous papers have appeared in journals and presentations have been made at countless professional meetings by the faculty.

The department has had an approved Accreditation Committee for Graduate Medical Education (ACGME) residency training program since 1966. The number of residents in the program during the last 25 years has varied from 24 to 30, depending on the number of affiliated hospitals involved. The program strives to provide exposure to all aspects of the specialty of PM&R. In the past there has been a major emphasis on management of inpatients with physical disability, but given the changing nature of medical practice, the program is currently being restructured, with the major emphasis to be on training in the outpatient setting.

It is regrettable that Mount Sinai medical students have little exposure to the field of PM&R, and the little they receive is through lectures provided by the faculty to third and fourth year medical students in August of each year, and through electives. There is a strong feeling among the department's faculty that PM&R requires designated time in the curriculum of the medical school, preferably by developing a required rotation of medical students through the department, where they would be exposed to patients with physical disabilities and musculoskeletal disorders. From 1978 to 1998, the residency training program was directed by Jerry Weissman, M.D., from Elmhurst Hospital. Adam Stein, M.D., is the current director of this program.

The Future

Like most branches of medicine, the field of PM&R currently is facing numerous uncertainties. However, it is clear that the fundamental needs of persons with disability will not change, and that their rights are now legally protected with the passage of the Americans with Disabilities Act. The elderly population will continue to grow and more lives will be saved after injury and disease. This means that there will be more people with diminished functional skills, and therefore there will be increased need for rehabilitation services. In delivering these services, accountability will increase, i.e., optimal results will have to be produced at the lowest possible cost. New and different levels of inpatient and outpatient rehabilitation services must be created, each different in scope, focus, intensity and, very important, in cost. The services must operate in a continuum of care, convenient and accessible to all patients in need. Collaboration with partners within the Mount Sinai-New York University Medical Center Health System is likely to increase, building new rehabilitation programs, and coordinating these programs into a network of rehabilitation services where high quality of care goes hand in hand with effective delivery. The recent merger of Mount Sinai with New York University Medical Center, with its world-renowned Rusk Institute of Rehabilitation Medicine, will predictably create new challenges and opportunities in clinical service delivery, education and research. Research must continue in order for us to find new ways to reduce physical disability and, in collaboration with our colleagues in the basic sciences, to find a cure for paralysis. Education of students, residents, various health professionals, and the public must be focused and effective in order to increase their understanding of the needs of people with disabilities and effective treatments. While these are ambitious goals, few if any institutions are more likely to achieve success in this field than the merged Mount Sinai-NYU Medical Center, with its two formidable departments of rehabilitation medicine.

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Geriatrics and Rehabilitation Medicine:

Common Interests, Common Goals

RICHARD A. FRIEDEN, M.D.

Abstract

Geriatrics and rehabilitation medicine are both fields with roots in antiquity, and they are both objects of renewed interest in modern times. They share a common philosophy: concern for the total needs of the patient. Both fields employ a team approach to patient care. The rehabilitation medicine physician (physiatrist) has an important role in the care of the elderly. Geriatricians and physiatrists should work together for research purposes and to improve the prevention and treatment of illness and disability in the aging population. **Key Words:** Geriatrics, rehabilitation, exercise.

History

THERE ARE HISTORICAL PARALLELS in the development of the fields of geriatrics and physical medicine and rehabilitation (PM&R). Both specialties can trace their roots to antiquity. Both areas deal with populations whose needs have not been met by past models of Western medical care.

References to aging and debility are found in writings from ancient Egypt, India, and China. The Greek physician Hippocrates and the Roman physician Galen made many observations on the process of aging and on the ability of some people to age successfully. Their works were incorporated into European thinking over the centuries (1).

Physical medicine (the use of physical agents as treatment modalities) and therapeutic exercise were discussed by Hippocrates (2). Both subjects developed over the centuries with more or less increasing scientific interest and acceptance. However, the popular view of the disabled and the perceived need for a field of rehabilitation medicine went through changes similar to that of the popular view of the elderly and the perceived need for a field of geriatrics. Physiatrists and geriatricians function as advocates for their respective patient groups.

Common Philosophy

Geriatrics and rehabilitation medicine share a common philosophy: the consideration of the "total person," i.e., observing the effect of disease or injury on all aspects of a person's life and functioning, and intervening wherever possible. Furthermore, both fields seek to prevent functional deterioration and stress the need for long-term planning and follow-up.

To accomplish these goals, both specialties employ the multidisciplinary or interdisciplinary team approach. The multidisciplinary method involves team members pursuing parallel tracks in patient care, meeting periodically to assess progress and modify goals. The interdisciplinary model sets common goals for the team members, each contributing to the work in progress in an overlapping and complementary fashion.

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The constitution of the team varies with the needs of the patient. It may include doctors, nurses, physical therapists, occupational therapists, social workers, psychologists, and other clinicians whose contributions may be of value.

Geriatrics, Disability, and the Physiatrist

An older patient is more likely to become deconditioned during a shorter period of time in bed than a younger person. When one considers the effects of prolonged bed rest on the elderly (especially the decline in exercise tolerance) (3) and the paucity of objective signs on examination or of complaints of distress by the patient (4), it becomes clear that the elderly are particularly prone to the complications of immobility. A higher index of suspicion is necessary, coupled with the need to anticipate potential problems earlier. Rehabilitation is an important part of both the assessment and treatment of these patients.

Physiatrists can bring many strengths and abilities to the aid of the elderly:

- Physiatrists can function as educators. In an academic setting, they give lectures to students, house staff, attending physicians, therapists, nurses, and other hospital personnel. In the clinical setting, they may give talks on subjects such as body mechanics, exercise, footwear, common types of injuries, and specific diseases to members of the community, patient support groups, and the press.

- Physiatrists are consultants. They are called in by physicians in other specialties to examine patients and render opinions regarding future outcomes, prevention of further disability, care of current impairments, potential admission to an inpatient rehabilitation unit, equipment needs, or possible post-acute care needs.

- Physiatrists are patient advocates. Due to their "global" focus, they may identify other aspects of the patient's care which need to be addressed. They bring these other issues to the attention of the primary care physician, educate patients and their families as to the nature of the condition, and reinforce their right to seek treatment—even by alternative or complementary methods. They communicate with social workers, insurance companies, and managed care agencies to arrange cost-effective care. They encourage creative thinking, to make the system work on behalf of the patients.

- Physiatrists can be team leaders. Some clinicians think of physiatrists' role in the interdisciplinary team as coordinators of care, like case managers. For many patients, the responsibility for much of what happens in the course of patient treatment rests with the physiatrists. They function in the coordination role and in the leadership role by encouraging communication among care givers, helping focus the care, solving problems, and monitoring outcomes and cost-effectiveness.

- Physiatrists are also researchers. Clinicians may write case studies or formulate trends, based upon empirical data collected on patients in their practices. Academicians may engage in benchwork hypothesis testing while experimenting in a lab or may pursue research on the wards, collecting data on a series of patients arranged for intervention in a randomized, double-blinded fashion.

- Physiatrists can relieve pain. They use oral medications, injections, exercises, problem solving, meditation, breathing and relaxation methods, supports such as canes, walkers and orthoses, acupuncture, and physical agents as mentioned earlier.

- Physiatrists give hope. They are in the business of optimism. This is not to say that they are unrealistic. They believe in accurate assessment of the patient's current status and emphasize what can be accomplished with training. In general, they do not believe in withholding resources because of doubts as to future potential. This fits in with their role as patient advocates.

One combination of the clinical and the patient advocate role is their involvement in palliative care for the frail elderly person, or the demented person, or the patient with a terminal illness. Physiatrists use their creativity to muster the resources needed for comfort and prevention of side effects and complications. They occasionally become involved in ethics and quality-of-life discussions.

A physiatrist needs to think "outside the box." Certainly, creativity and the ability to think of innovative ways to treat patients and help them attain benefits are qualities that are not limited to physiatrists. However, those who do possess these qualities tend to achieve better results for their patients and tend to foster creativity in other members of the team.

Rehabilitation Medicine and the Geriatric Patient

Inpatient Needs

The physiatrist has had a long-established role in the care of the hospitalized patient. Whether in the acute care or subacute care settings, the physiatrist establishes diagnoses, assesses pre-admission functional status, estimates post-discharge needs, and coordinates education, remobilization, and functional interventions during and after discharge. In the long-term care setting, the physiatrist monitors patients periodically for potential decline in function, to provide intervention as early and as rapidly as possible.

Outpatient Needs

The involvement of physiatrists in the care of the patient outside the hospital setting has been a fairly recent development. In the ambulatory care setting, the physiatrist may continue the broad approach to the comprehensive functional needs of patients. However, there is an increasing need for rehabilitation physicians to provide a narrow focus for a particular complaint, especially in the area of sports medicine. Their more vigorous elderly patients also require this approach.

As part of the elderly population becomes less mobile and less able to seek help outside the home, there seems to be a resurgence of interest in "house calls." Home care agencies provide patient care based upon a doctor's prescription. The physiatrist has several roles in this system. They include visiting the homebound patient, prescribing and coordinating care, and fostering communication among health care providers, patients, and relatives.

Thus, physiatrists can and should play an important role in patient care throughout the post-hospitalization period. They can not only develop clinical pathways for patient management in the post-acute setting, but can also function as "gatekeepers" for delivery of care (5).

The Need for Closer Interaction

With so many changes happening in the modern health care system and with resources being apportioned with increasing parsimony, it is important to note that much research in areas common to both geriatrics and PM&R occurs on parallel tracks.

Perusal of the geriatric and PM&R literature confirms this tendency. For example, osteoporosis and the effects of exercise have been studied by physiatrists (6, 7) as well as by geriatricians (8, 9). Management of elderly patients who have had hip fractures is another area of interest common to both geriatrics (10, 11) and PM&R (12, 13). Assessment of balance and prevention of falls is a third area in which investigators in both PM&R (14 – 17) and geriatrics (18 – 21) have taken active roles.

Need for Common Terminology

There are a few research areas in which not only is effort duplicated, but also terminology differs to the extent that it is sometimes difficult to compare results. One example is the "sit-to-stand" test (STS), also known as the "chair-rise" test in much of the geriatric literature.

The ability and/or speed required to rise unaided from a chair has been incorporated into several testing batteries, and the results extrapolated to leg function, walking ability, and self-care ability (22, 23). However, the experimental setting (especially the design specifications of the test chair [24, 25]), the acquisition of data, and the analysis of results are highly variable. Data are cited to prove that the strongest predictor of successful chair rise is lower extremity strength (26). Other studies cite the starting position of various joints (27), the motions of the joints (28), or the ability to coordinate the actions of various muscles during phases of the test (29). Comparison of these studies reveals similar graphs with similar results, but different labels and phases.

A common terminology would help decrease confusion when readers attempt to derive conclusions from testing and treatment protocols. Interdisciplinary research protocols would be simplified.

Suggested Focus Areas for Investigation

Disability with Aging and Aging with a Disability

Further work is needed on the quality of life of the increasing numbers of patients with orthopedic and neurologic impairments who are surviving into old age. Another area of concern is the development of musculoskeletal complications which arise from disorders acquired during youth, such as shoulder degeneration in persons with paraplegia.

There are also some conditions which may continue to evolve over time, such as recovery from stroke. As patients may show gradual improvement over a long interval, it is important to prevent complications during this time, to detect the improvements in a timely manner, and to use these changes to increase function. Patients so affected require periodic monitoring and occasional intervention. The notion of the "plateau" should be re-evaluated, especially in light of the theories of brain plasticity. Furthermore, there is very little information available regarding management of patients 10 to 20 years after an adult-onset event.

Fitness

In recent times, there have been increased efforts to promote fitness and strength training in the aging population—at home, in the gym, and in health care facilities. Biochemical and histological studies of older participants have shown that their skeletal muscles will respond to exercise (8, 30, 31). However, improving fitness does not necessarily lead to functional improvements. The best way to improve gait or self-care is by training specifically for that function (32).

Changes with Aging—Are They Reversible?

Gerontologists have long sought a biomarker of the aging process. However, many body systems that are affected by disease or disuse are not considered useful for this purpose. One group of researchers has reported that the decline in Maximum Oxygen Consumption (VO_{2max}) with aging seems to reflect changes due solely to the aging process. They concluded not only that exercise performance correlates well with measurement of Vo_{2max}, but that VO_{2max} is a reliable marker of "successful" aging (33).

Other studies have shown that normal aging causes a gradual reduction in activity and function. The observed reduction in exercise tolerance is more often related to changes in body composition, rather than to deterioration in cardiac function. Aging muscle uses oxygen less efficiently, which in part has been attributed to mitochondrial dysfunction. This metabolic change responds favorably to training, just as it does for the younger population (34–36).

After conducting a meta-analysis of 29 studies of the effects of endurance training on functional capacity in the elderly, one group of authors concluded that there is a significant benefit. Increases in functional capacity are related inversely to subject age and directly to duration of exercise bouts, length of the training regimen, and pre-training VO_{2max} (37).

In 1993, Drs. Mary Fiatarone and William Evans published an article advocating resistance training and nutritional supplementation to reverse dysfunction in aging muscle (35). They followed this report with a 1994 study which showed that elderly exercisers who received nutritional supplementation responded the best, followed by exercisers who did not receive nutritional supplements. Those who received nutritional supplements but did not exercise did not improve in physiological or functional parameters (38).

The effects of long-term exercise are being studied (8, 39). Another important research question is the relationship between strengthening anti-gravity muscles and preventing falls (40). Various authors have achieved postural influences by shoulder girdle strengthening, by lower extremity strengthening, and by water exercises (41).

The *Archives of Physical Medicine and Rehabilitation* has published numerous studies over the years concerning exercise and the elderly (6, 15). Beneficial effects include increased gait velocity (42), sustained favorable lifestyle modification (43), decreased sway, and shorter reaction times (44, 45), in addition to the expected increases in strength.

Falls, Balance, and Posture

A joint initiative between geriatrics and PM&R is also needed to study falls and injury prevention.

There are many patient (intrinsic) and environmental (extrinsic) factors that contribute to falls and injury (46, 47). Analysis of this problem usually begins with the patient, often after multiple falls and injuries have occurred.

As regards intrinsic factors, published reports have cited static balance, lower extremity strength, ankle and hip flexibility, joint position sense, and cerebellar function. Thus, both peripheral and central mechanisms are involved. Postural disturbances, reduced muscle strength, slower reaction times, stiffer connective tissue, and less dense bones also contribute to falls and injury.

The second main area of concern in preventing falls and injury is systematic environmental assessment. Much can be done to maximize safety and independence, whether clients reside in nursing homes, chronic care facilities, or private homes. This includes the presence of alarms, adequate lighting, and adaptive equipment (e.g., grab bars, bath equipment). Special attention should be paid to coordination of furniture dimensions and functions. Rugs and room thresholds are potential hazards for ambulatory patients. The environmental assessment should be incorporated into the home visit protocol.

Thirdly, dependence in activities of daily living is associated with increased falls risk. For example, transfer activities are essential for safe mobility of the dependent, nonambulatory patient. Particular attention must be directed toward furniture positioning, appropriate footwear, clear instructions to the patient, and good body mechanics on the part of the care giver. Transfer activities must be modified after lower extremity surgery, especially to avoid dislocation of a hip arthroplasty.

One of the best-known researchers in the geriatric and internal medicine literature in the field of prevention of injurious falls is Dr. Mary E. Tinetti. She has criticized the disease-oriented approach to assessment of mobility problems (46). Tinetti prefers the performance-oriented approach, asserting that "falling is an entity in its own right, most commonly due to the accumulated effect of multiple chronic disabilities, and that it may be preventable if the causative factors are recognized in individual patients." (48).

Tinetti has also sought to improve upon laboratory gait analysis, which does not give a true picture of mobility in one's usual environment (46). She has been able to prove that her analysis method, combined with appropriate intervention, has a beneficial effect (49).

One cannot leave the areas of exercise, balance, and falls without a brief consideration of the "Frailty and Injuries: Cooperative Studies of Intervention Techniques" (FICSIT) trials (50). It involved more than 2,400 volunteers participating in various interventions. A group of eight centers around the country pursued different clinical trials, using similar data-collection methods.

A meta-analysis attempted to account for all seven independent, randomized, controlled trials—two in nursing homes and five community-based. Each facility included some form of exercise in its interventions, but this varied in duration, frequency, and intensity. The main conclusion was that the adjusted fall incidence ratio was slightly lower for the programs that included balance training (0.83) than for those that included exercise training (0.90). Further analysis suggested that a program that includes t'ai chi is of particular benefit in lowering risk. Many other variables existed, since the programs were not uniform in their composition (51).

Exploration of Complementary Medicine

Another area which PM&R and geriatrics researchers should explore jointly is the benefits and applications of complementary medicine. Patients are gathering information from the media (especially via the Internet) and from the community at large regarding herbal treatments, physical agents (such as magnets), and various movement techniques. These areas should be studied and the scientifically validated therapies should be incorporated into evaluations and treatments.

One example of such a therapy is t'ai chi chuan. This is a Chinese "soft," or internal, martial art. This means that t'ai chi uses soft, slow, flowing motions that develop awareness, coordination and inner harmony. Since it also fosters relaxation, it has been used as a means of dealing with stress and tension.

T'ai chi has been reported to have many benefits, including increasing joint mobility, improving circulation, lowering blood pressure, reducing back pain, bolstering the immune system, improving athletic performance, and aiding weight reduction. It has been previously noted that t'ai chi has a beneficial effect on the responses of the cardiovascular and pulmonary systems to exercise (52), and that its practitioners perform better on tests of balance than do non-practitioners (53).

As a result of the FICSIT trials, interest has increased in the use of t'ai chi for reduction of falls (51). Two of the centers which used t'ai chi during FICSIT have published their results separately, so one can analyze their interventions in greater detail (54–57).

Functional Outcome Measurement

The latest area to be explored in geriatric rehabilitation is outcome measurement. Traditional rehabilitation models of assessment (58) and public health models (59, 60) are being applied. Clinical practice guidelines are being developed (61), in the hope that greater efficacy can be combined with cost-effectiveness in the delivery of care. These new initiatives require the combined input of both geriatricians and PM&R physicians.

Conclusions

Articles summarizing the philosophies, approaches, and delivery models of geriatric rehabilitation have been published in several journals (62–65). Several textbook chapters explore this material in varying amounts of detail (66–68).

One particular example of collaboration between clinicians and researchers in geriatrics and rehabilitation medicine is an entire textbook devoted to the subject, published in 1994 (69). The interested reader is referred to these sources for more information.

As more people age and enter the pool of the potentially disabled, the importance of both geriatrics and PM&R increases. Both fields are experiencing growth. However, they must work together to define their roles more clearly, apply similar terminology for clarity of communication, conduct joint research projects to validate their efficacy with similar methods, hold joint grand rounds in topics of mutual interest, and in general share their common vision for the best possible care of the aging population.

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Physiatric Management of Mild Traumatic Brain Injury

Steven Flanagan, M.D.

Abstract

Mild traumatic brain injury (MTBI) is a common condition, afflicting as many as 1.5 million Americans yearly. Most individuals sustain MTBI as a result of motor vehicle collisions, but it may also occur as a result of falls, physical assault or sporting accidents. Problems related to MTBI include various pain syndromes, cognitive impairments, disorders of affect, cranial nerve dysfunction, and vertigo, arising from injury to the brain, head, or cervical spine. Symptoms are usually transient, although a small percentage of afflicted individuals develop long-lasting problems, often preventing them from leading productive lives. Recognition of these problems as arising from MTBI is difficult due to the frequent lack of abnormal findings on diagnostic tests and failure to identify a history of head trauma. The American Congress of Rehabilitation Medicine has defined MTBI, an important first step in identifying individuals who need treatment. Diagnosis is usually made by directed questions regarding trauma history and careful procurement and interpretation of appropriate tests. Once a diagnosis is made, proper care can be prescribed in order to lead patients toward more productive lives.

Key Words: Traumatic brain injury, rehabilitation.

Epidemiology

Traumatic brain injury (TBI) is a serious health concern, accounting for 500,000 hospitalizations per year in the United States, the vast majority of which are referred to as mild or minor injuries (1). These figures, however, underestimate the true incidence of mild TBI (MTBI), as there are as many as 1.5 million occurrences of transient loss of consciousness in the United States yearly that do not result in hospitalization (2). Many more individuals sustain mild head injuries as a result of sporting or recreational accidents, with at least 250,000 concussions occurring yearly in high-school football alone (3). The extent to which mild brain injuries represent a severe health concern is underscored when one considers that for every head injury fatality, there are 27 individuals injured but not hospitalized. This alone accounts for an incidence of 1.5 million cases of mild TBI per year (4). Many individuals never seek medical treatment, contributing to the lack of accurate epidemiological data (5, 6). Mild TBIs are most commonly due to motor vehicle collisions, although a large percentage arise from sporting or other recreational activities, with still fewer occurring as a result of assault. Symptoms of mild TBI are usually transient, often lasting only a few seconds, although many individuals experience persistent symptoms, including pain, dizziness, hearing loss, olfactory and gustatory loss, visual disturbances, behavioral disorders, and impaired cognition. Accurate diagnosis and treatment require recognition of these sequelae as arising from mild TBI.

Terminology

"Mild traumatic brain injury" is a term that causes confusion for health care providers. Numerous terms have been used in the past, but

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they lack a cohesive definition or a set of criteria that effectively distinguishes minor brain injuries from more severe trauma. "Concussion" is the most commonly used term to describe these injuries, but definitions vary widely in both specificity and severity. Mild head trauma has also been referred to both as "trivial head injury" (7) and "minimal head injury" (8), suggesting that no adverse sequelae result. Some researchers have attributed the symptoms of mild head trauma to post-traumatic stress disorder (PTSD), which is a specific psychiatric disorder that must meet DSM 4 criteria and is not synonymous with MTBI. Others have used either accident or compensation neurosis to describe individuals sustaining minor injuries (9, 10). These terms denigrate the legitimate and often long-lasting symptoms of those truly afflicted and should be used cautiously, if at all, by health care providers.

Despite the varied definitions, "concussion" remains the most frequently utilized term to describe mild brain injuries. As part of an effort to better define the term as well as to improve treatment, the Quality Standards Subcommittee of the American Academy of Neurology established a definition of "concussion" which also describes its severity. "Concussion" is defined as a traumatically induced alteration in mental states, which may or may not result in unconsciousness (11). The two defining components of concussion are confusion and amnesia, which may occur immediately after the blow to the head (12) or several minutes later (13). Confusion is manifested as distractibility, inability to maintain coherent thoughts or carry out goal-directed movement, or a disturbance of vigilance (14). Concussion severity is based on duration of symptoms following the injury as well as the presence or absence of unconsciousness. The details are provided in Table 1. This grading system has been utilized to determine whether athletes sustaining a head trauma should seek additional medical treatment prior to considering resumption of competition (11).

The Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine has established "mild traumatic brain injury (MTBI)" as the preferred term for concussions. Specific criteria were established to distinguish MTBI from more severe forms of TBI (Table 2). While this definition is similar to the one provided by the American Academy of Neurology, it better differentiates mild from more severe head trauma. A grade 3 concussion is no longer considered mild when unconsciousness persists beyond 30 minutes, the Glasgow Coma Score (GCS) falls below 13, or if post-traumatic amnesia persists beyond 24 hours. The definition includes those individuals sustaining either a direct blow to the head or

TABLE 1

Concussion

Definition

A traumatically induced alteration in mental state that may or may not result in unconsciousness.

Grade 1 Concussion
1. Transient confusion
2. No loss of consciousness
3. Concussion symptoms or mental status abnormalities on examination resolve in less than 15 minutes.

Grade 2 Concussion
1. Transient confusion
2. No loss of consciousness
3. Concussion symptoms or mental status abnormalities on examination last more than 15 minutes.

Grade 3 Concussion
1. Any loss of consciousness, either brief (seconds) or prolonged (minutes).
   (A) mild brain injury
   (B) moderate brain injury
   (C) severe brain injury

TABLE 2

Mild Traumatic Brain Injury

Definition

A traumatically induced physiological disruption of brain function, as manifested by at least one of the following:

1. any period of loss of consciousness;
2. any loss of memory of events immediately before or after the accident;
3. any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and
4. focal neurological deficit(s) that may or may not be transient.

but where the severity of the injury does not exceed the following:

1. loss of consciousness of 30 minutes;
2. after 30 minutes, a Glasgow Coma Score of 13-15; and
3. posttraumatic amnesia not greater than 24 hours.

This definition includes:

1. the head being struck;
2. the head striking an object; and
3. the brain undergoing an acceleration-deceleration movement without external trauma to the head.

This definition excludes stroke, anoxia, tumor, encephalitis, etc.

Developed by the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine.

an acceleration-deceleration injury to the brain. It excludes those individuals meeting the criteria due to stroke, anoxia, tumor, infection or seizures. While this definition has the most specific criteria thus far, situations in which MTBI arise are rarely medical emergencies, so patients often do not seek acute medical treatment. Hence, medical documentation of the criteria is often lacking, so it is appropriate to consider the constellation of symptoms described by patients in making the diagnosis of MTBI.

Pathophysiology

The pathophysiology of MTBI differs from that of more severe cases in both the degree and location of the lesions, but not in the nature of the injury. Animal and human studies have documented similar neuropathological lesions in the brains of individuals sustaining mild brain trauma as those with more severe injuries. Advances in neuroimaging, specifically magnetic resonance imaging (MRI), have allowed investigators to view structural lesions not previously viewed with older radiographic techniques (15, 16). Furthermore, neurobehavioral disturbances have been correlated with specific lesions in the frontal and temporal lobes on MRI. These disturbances resolve as the imaged lesions disappear (17).

Pathological lesions following TBI may be classified as either focal or diffuse. Focal lesions include lacerations, contusions, focal ischemic or hypoxemic injuries, and basal ganglia hemorrhages. They often occur as a direct result of blunt-instrument trauma to the head, resulting in skull fractures, intracerebral hemorrhages such as subdural hematomas, dural or cerebral lacerations, and contusions. Contusions, caused by the brain moving within the cranial vault and striking the interior portion of the skull, are most often located in the inferior frontal and anterior temporal lobes, accounting for disturbances in both executive function and affect. Focal hypoxic lesions and basal ganglia hemorrhages cause local abnormalities, but usually arise in the setting of more diffuse injuries arising from acceleration-deceleration injuries. The hippocampus is extremely sensitive to hypoxemia, accounting for the frequency of memory impairments following TBI.

Much has been published regarding the process of traumatically induced neuronal injury caused by the release of excitatory amino acids. Numerous animal models have demonstrated massive increases in extracellular levels of glutamate, aspartate, and acetylcholine immediately following TBI. This initiates a process leading to increased intraneural calcium and the development of highly reactive oxygen radicals, causing lipid peroxidation of the cell membrane and ultimate neuronal demise. This process has been experimentally demonstrated in both mild and severe cortical injuries (18) and is likely a cause of functional impairment regardless of injury severity.

Diffuse axonal injury (DAI) was first described in the early 1980s as a process causing diffuse neuronal injury. It arises from shearing forces occurring in acceleration-deceleration injuries (19, 20), causing damage to white matter tracts. Originally, DAI was described as occurring in only the most severe cases of TBI, accounting for poor outcomes such as coma and vegetative state. However, DAI has also been found in MTBI, both in animal models (21, 22) as well as in postmortem examinations of individuals succumbing to other, more serious injuries (19, 23, 24). It has become evident that a spectrum of DAI exists, in which neuronal damage occurs due to axonal stretch, but that neuronal injury differs in both the amount and location, based on severity of the insult. Accordingly, four stages of DAI have been described, ranging from mild transient alteration of axonal function, to immediate axotomy resulting in coma (25). Stage I DAI describes a process of transient ionic fluxes occurring primarily at the node of Ranvier when the axon is subjected to no more than a 5% stretch of its resting length. Generation and propagation of action potentials are halted, although lasting only several minutes. Stage II DAI occurs with a 5-10% stretch, resulting in ionic fluxes described for Stage I, but which reach a metastable state. Osmotic forces cause localized swelling and possibly mild alteration in axoplasmic transport. The disturbances are transient and axon structure returns to baseline without ultimate axotomy. Stage III DAI occurs when the axon sustains a 10–20% stretch. Normal ionic equilibrium can no longer be restored, resulting in cytoskeletal injury and severe impairments in axonal transport. Severe localized swelling follows, impairing structural integrity of the cell membrane, both of which cause axotomy 24–72 hours after the initial impact (26). Stage IV DAI occurs with a greater than 20% stretch, resulting in primary axotomy. Location of DAI in part depends on the severity of injury; it occurs primarily in subcortical white matter areas in MTBI and in the corpus callosum and brainstem in severe TBI.

Diagnosis

Appropriate diagnosis of MTBI is challenging. Those afflicted with the sequelae are often misdiagnosed as malingerers, symptom exaggerators or neurotics, or those suspected of being in search of secondary gain. The failure to make a proper diagnosis is due to many reasons, including the frequent paucity of focal neurological abnormalities, failure of both the clinician and the patient to attribute signs and symptoms to a brain injury, and lack of both medical documentation at the time of the injury and objective abnormal findings on diagnostic studies. This difficulty in diagnosis has led many clinicians to doubt the existence of MTBI as a clinical entity, fostering a belief that those complaining of symptoms are malingering. Furthermore, many symptoms following MTBI are not directly a result of brain injury, but are due to whiplash, which often accompanies brain trauma.

Despite these challenges, it is appropriate to consider the symptoms reported by a patient, the situation in which the injury occurred, and physical examination findings, as well as results of diagnostic tests when making a diagnosis of MTBI. Symptoms most often reported by individuals with MTBI include headaches, memory disturbances, dizziness, and weakness, frequently occurring in combination (27). Clinicians should be cautious before solely accepting self-reported symptoms when making a diagnosis, since patients without head injury are remarkably astute in accurately describing these symptoms (28). An accurate diagnosis must include a reasonable etiology of the injury as well as satisfy the definition set by the American Congress of Rehabilitation Medicine described earlier. One should not diagnose MTBI if a period of altered mental state did not exist at some time surrounding the injury. Routine diagnostic tests are often unrevealing. Computerized tomography (CT) is frequently normal, in part because scanning usually occurs after the acute phase, since most cases of MTBI are not medical emergencies. Magnetic resonance imaging is more sensitive than CT in detecting subtle lesions than CT, including white matter lesions arising from DAI (29–31). MRI is the preferred neuroimaging modality in non-emergent situations, although here as well, results are often unrevealing even when MTBI has occurred.

Additional tests may help support the diagnosis. Positron emission tomography (PET) may provide evidence of cerebral dysfunction in the absence of detected structural lesions on CT or MRI. PET findings are not by themselves universally accepted as accurate in detecting cerebral lesions following trauma, although they do have added significance when findings are correlated with abnormalities on neuropsychological examination or other imaging tests. Single photon emission computerized tomography (SPECT) is more sensitive in detecting cerebral injury following MTBI than standard CT (32, 33). Electroencephalography is most often normal following MTBI, although abnormalities in the absence of preexisting neurological disease provide supportive evidence for diagnosis. Evoked potentials, posturography, and formal assessments of olfactory and gustatory function may lend additional supportive evidence in certain cases.

Neuropsychological testing is often the only reliable measure supporting the diagnosis. Deficits in executive function, attention, concentration, processing speed, and memory are often found on testing in individuals who have persistent complaints of cognitive dysfunction. The fact that neuropsychological test results are often the only positive findings is potentially problematic, as poor test performance may be intentional on the part of the individual examined. Careful interpretation of test results as well as of test behaviors is critical in order to ensure that a proper assessment has been made.

Although abnormal focal neurological findings may be lacking, they may also be overlooked by an unsuspecting clinician. Findings suggestive of any diagnosis may be missed if they are not specifically sought out on history and physical examination. This is particularly true with MTBI. A full neurological evaluation is imperative, including assessment of all cranial nerves. Olfactory disturbance, for instance, has been found in up to 40% of all TBI cases in one study (34), yet is neither inquired about nor tested for in most examinations. In general, however, as is often the case in medicine, careful attention to history, physical examination, and appropriate procurement and interpretation of diagnostic procedures will lead the clinician to the proper diagnosis.

MTBI-Related Conditions

Cognitive Impairments

Cognitive impairments following MTBI are usually transient. Areas of impairment are generally similar to those in more severe injuries, and include problems with attention, concentration, processing speed, executive function and memory. Complaints are more common immediately following the injury (35 – 38), but in the vast majority of cases the impairments spontaneously resolve, allowing the return to normal daily functioning. When impairments are persistent, they may be subtle, becoming apparent only during times of increased cognitive demand (39). Repetitive MTBI results in more persistent cognitive impairments (40), which is an important consideration when allowing an injured athlete to return to competition.

The array and severity of cognitive impairments reported in the literature may cause some confusion regarding the exact nature and extent of the problem. This is in due part to the considerable variability in patient selection and to the design of the various studies. A recent meta-analysis of studies examining this issue revealed that patients with MTBI demonstrate subtle impairments, most commonly in attention, but suggested that clinicians would be more accurate in not diagnosing a brain injury on the basis of neuropsychological test results than in diagnosing a brain injury (41). The studies selected for this review included only those in which patients were not preselected on the basis of symptoms, and therefore its finding is consistent with the fact that most cognitive impairments are transient.

Individuals with persistent cognitive complaints should be referred for neuropsychological testing in order to identify specific areas of cognitive weaknesses as well as to determine areas of preserved strength. Careful interpretation of data is essential and should be compared with expected pre-morbid capability, which is based in part on the educational and vocational history of the individuals afflicted. Goals of cognitive remediation are to develop strategies using preserved strengths in order to compensate for areas of weaknesses. Successful remediation requires patient and family education on both the test results and compensatory strategies developed.

Disorders of Special Senses

Visual, auditory, olfactory, and gustatory disturbances occur in varying degrees following MTBI. Visual impairments manifest as oculomotor and accommodative dysfunction as well as visual field loss. Individuals sustaining MTBI experience difficulty with refraction, near point convergence and stereo acuity (42). Optometric evaluation and treatment should be sought for individuals with visual complaints, as visual rehabilitation has been shown to objectively improve function following MTBI (43).

Olfactory dysfunction occurs in up to 40% of all cases of TBI (34). The three pathophysiological mechanisms of olfactory injury in head injury include damage to the nasal passages, shear injury of the olfactory nerve, and cortical contusions. If recovery of olfaction does not occur within the first 12 months following injury, prognosis for this sensory modality is poor (44). Patients must be asked about olfactory loss, as they often will not offer it as a complaint, even when present. When testing olfactory function, it is necessary to avoid noxious stimuli that may inadvertently stimulate the trigeminal nerve, possibly resulting in a false negative response. True gustatory loss is rare, and when present, is most often due to olfactory injury.

Whiplash-Related Injuries

Many sequelae of MTBI are not directly related to cerebral injury, but rather to concurrent trauma to extracranial structures. Whiplash frequently accompanies head trauma, particularly in motor vehicle collisions, but also in cases of blunt-instrument trauma and recreational or sporting accidents. Many complaints following MTBI are due to pathological lesions in peripheral nerves, muscles, and vascular structures in the head and neck. Whiplash, which results from forceful cervical flexion-extension, with or without a torsional component, may result in clinical situations that manifest as neck or head pain, reduced cervical range of motion, autonomic dysfunction, and visual disturbances. Although not directly related to brain trauma, whiplash-related injury is included in the discussion of MTBI due to the frequency with which it is a co-morbid condition.

Headaches

Headaches are the most frequent acute and chronic somatic complaint following MTBI (27). Although headaches in the acute phase may be a result of subdural or subarachnoid hemorrhage, the vast majority of post-traumatic headaches are due to head and neck injuries. They are due most often to musculoskeletal injuries, followed by nerve entrapment or injury, vascular disorders, and less frequently to autonomic dyscontrol (45). Accurate diagnosis of post-traumatic headaches relies heavily on history and physical exam finding, and little on diagnostic tests. Accurate assessment requires an understanding of the various etiologies of headache, in order to recognize both the common and the unusual causes.

In 1942, Simons and Wolff (45) proposed a classification system for post-traumatic headaches that is still useful today. In this scheme, headaches are classified by the affected anatomical structure and include those arising from musculoskeletal trauma, nerve entrapment, vascular injury, or dysfunction in autonomic control. This scheme aids the clinician in systematically identifying the etiology of headaches by exploring common as well as obscure causes of cephalalgia. Despite the infrequency of cerebrally mediated causes of headache, pain associated with focal neurological findings, nausea, or vomiting should prompt an urgent work-up, including appropriate neuroimaging techniques.

Musculoskeletal Induced Headaches. The vast majority of post-traumatic headaches arise from injuries to muscles in the neck, shoulders and head, and have been reported to be present to some degree in nearly all cases in one series (45). "Myofascial pain syndrome" describes a condition characterized by muscle pathology in which tenderness is palpated in a muscle over a taut band of fibers. The pain radiates to a specific but remote body region. This tender area is known as a trigger point (46, 47). Individuals with myofascial pain describe a sensation of steady pressure that may be either mild or severe. It may be exacerbated by physical exertion, forward bending, or valsalva. Associated symptoms may include photophobia, dizziness, and a sense of unsteadiness.

Myofascial pain syndrome most often arises in head trauma in the setting of whiplash. Flexion-extension injuries of the cervical spine produce stretch injuries to muscles, which may ultimately result in the development of trigger points. The muscles most susceptible to injury include the trapezius, sternocleidomastoid, splenius capitus, splenius cervicus, temporalis, levator scapula and the scalenes. The mainstay of treatment is injecting the trigger point with a local anesthetic. Spraying the skin overlying the muscle with a topical cooling agent, followed by stretching of the involved muscle, ischemic pressure over the trigger point, and various thermal modalities are all effective in treating myofascial pain (47). Work habits and posture need to be observed and abnormalities corrected. Nonsteroidal anti-inflammatory agents and tricyclic antidepressants may provide additional relief. Tricyclic antidepressants are particularly helpful with coexisting sleep disturbances. Individuals afflicted need to be instructed in a home exercise program, including stretching and limbering maneuvers, in order to maintain the relief obtained with the foregoing measures.

Neurogenic Headaches. Headaches arising from entrapped or injured peripheral nerves comprise the second most common form of post-traumatic headaches (45). Pain arises from damage to a peripheral nerve either by entrapment in a scar formed at the site of impact or laceration, or in a nerve injured by excessive stretch occurring during whiplash. Pain is exacerbated by pressure over the nerve and has an electric or burning quality. The greater occipital nerve, which is the continuation of the second cervical root, is particularly vulnerable to stretch during whiplash. When injured, it causes pain over the posterior portion of the scalp. The greater occipital nerve may also be compressed as it pierces the semispinalis capitis or trapezius, which may themselves be injured in whiplash injuries. Treatment measures are similar to those used for other neurogenically mediated pain syndromes and include membrane stabilizers and various antidepressant drugs. Anesthetic infiltration in neuroma formation, as well as counterstimulation techniques, provides relief in many cases. However, attention must be directed to the possibility of coexisting myofascial pain, as this is present in nearly all cases of post-traumatic headaches, and successful treatment will not occur if it is overlooked.

Vascular Headaches. Migraine headaches are thought to arise from vascular dilatation and are described as dull and aching, often associated with nausea, vomiting, and anorexia. These headaches are rarely a direct result of trauma. Rather, they may be exacerbated following trauma in those previously afflicted (48). Recent evidence suggests that migraines following TBI may be due in part to alterations in electrolyte balance, release of excitatory amino acids, impaired glucose metabolism, and abnormalities in catecholaminergic and opioid function (49). Treatment of acute attacks is aimed at decreasing vasodilatation, while prophylactic treatment is provided by such drugs as beta-blockers, tricyclic antidepressants, and calcium channel blockers.

Dizziness

Dizziness is reported as the third most common somatic complaint following MTBI (27). Symptomatically, it ranges from a nondisabling perception of lightheadedness to incapacitating vertigo. Causes of impaired balance are numerous, due to the many central and peripheral systems involved in maintaining a normal upright position. Following TBI, dizziness is most often due to injury to the ear, although attention must be directed toward other causes, including peripheral neuropathies, complications from whiplash, musculoskeletal injuries, and vascular disorders. Accurate diagnosis requires a thorough understanding of normal vestibular function, as well as the possible etiologies of vestibular impairment following TBI. Most causes of post-traumatic dizziness can be determined through a detailed history and physical examination, although specialized tests, including electronystagmography, posturography, caloric irrigation, audiology and central nervous system imaging may be helpful in delineation of the precise etiology. Associated symptoms must be sought out, especially hearing loss and tinnitus, as individuals may not mention them unless specifically questioned.

Benign Positional Vertigo. Benign positional vertigo (BPV) is the most common neuro-otological disorder following closed head injury (50). It arises when calcium carbonate is dislodged from the macula of the utricle and reattaches to the cupula of the posterior semicircular canal. Diagnosis is usually made at the bedside by maneuvering the patient in provocative positions and assessing for nystagmus and vertiginous symptoms. BPV is usually self-limiting, and reassurance is often all that is needed. Persistent complaints should be treated with vestibular exercises under the guidance of a trained physical therapist. Pharmacological agents, including anticholinergic agents, benzodiazepines, and membrane stabilizers, may be helpful, although vestibular exercises alone are often more effective (51). As pharmacological agents mentioned may cause sedation and impair cognition, they should be used with caution in individuals who have sustained a TBI. Surgery may be considered as a last option in patients refractory to other treatments; it is successful in the vast majority of cases (52).

Temporal Bone Fracture. Dizziness associated with hearing loss and tinnitus occurs less commonly than BPV. Temporal bone fractures may result in both hearing loss and profound vertigo, which may be incapacitating. Suspected cases of temporal bone fractures must be assessed by a temporal bone CT scan, as they are easily missed on standard head CT scans and plain radiographs. Dramatic improvements may be observed with low dose benzodiazepine, although caution is urged in cases of both impaired arousal and cognition.

Hydrops and Fistulas. Endolymphatic hydrops and post-traumatic perilymphatic fistula (PTPF) are uncommon causes of vertigo. PTPF may be associated with mild nausea and headache, with hearing loss occurring as a fluctuating late complication. Hearing loss is a major component of endolymphatic hydrops. Treatment of both disorders involves discouragement of rapid changes in head position, and limited bed rest. Surgery is sometime indicated for endolymphatic hydrops, but rarely for PTPF.

Cervicogenic Dizziness. Cervicogenic dizziness is a controversial disorder in which dizziness occurs in the absence of vestibular injury. It is postulated to arise from injury to either the anterior or the posterior chain of cervical sympathetic nerves following whiplash (53) or compromise of vertebral-basilar blood flow (54). Injury to the anterior cervical sympathetics occurring in cervical hyperextension injuries may result in Bernard-Horner Syndrome. This causes dizziness with associated ipsilateral miosis, ptosis, and anhydrosis. Similarly, hyperflexion injuries may damage posterior cervical sympathetics. Known as Barre-Lieou Syndrome, posterior cervical sympathetic dysfunction is a controversial disorder and is considered rare even by those who support its existence. Theoretically, symptoms develop due to irritation of the posterior cervical sympathetics, which converge to form the vertebral nerve as well as the sympathetic plexus which surrounds the vertebral artery. Irritation may result in increased vascular tone, causing symptoms of vertebral-basilar insufficiency (55), which has been demonstrated in an animal model (56). Associated symptoms include tinnitus, occipital headache, impaired vision, and dysphonia (50). Therapeutic interventions are geared toward decreasing cervical dystonia and increasing cervical range of motion.

Conclusion

MTBI is a condition that occurs with alarming frequency, yet is often overlooked and misdiagnosed. Although the majority of individuals afflicted will experience transient symptoms, a significant minority will have persistent and sometimes disabling problems, preventing them from returning to previous lifestyles. Health care providers must be diligent in detecting the clinical signs associated with MTBI in order to properly diagnose and treat afflicted individuals. Careful attention to history and physical examination findings, as well as appropriate accrual and interpretation of diagnostic tests will ultimately lead the clinician to the proper diagnosis and treatment.

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Quality of Life as a Construct in Health and Disability Research

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Abstract

Definitional issues that affect the measurement of quality of life (QOL) in health care research are discussed. In reviewing a broad sample of health- and disability-related QOL studies, the authors note several characteristics in which respective approaches to measurement differ: (a) In various measurement tools, QOL has been located either within the insider's (i.e., the person being measured) judgment of the "goodness" of his or her life or outside this judgment. (b) The insider's and/or outsider's values may hold sway in deciding the elements of life that are relevant to QOL within the measurement process, and in rating the degree of "goodness" of these life domains. (c) QOL models incorporate domains of items varying in breadth and specificity; and they take either a negative or neutral view of functioning. (d) QOL models vary in their complexity, type of linkage between components, and inclusion (or not) of both the insider's judgment and external predictors of QOL. These distinctions are used by the authors in recommending approaches to QOL measurement suitable for health care research aimed at outcome assessment and description of populations. **Key words:** Quality of life, disability, chronic illness, research methodology.

In the United States, studies of quality of life (QOL) first came to the fore in the mid-1970s with the exploring of perceptions of subjective well-being within the general population (1, 2), as well as the use of more objective, community-focused "social indicators" (3, 4). More recently, interest in assessing health-related quality of life (HRQOL) has increased within health care research (5–8), particularly in studying outcomes of medical interventions and in tying increases in life quality to costs associated with medical care. Numerous QOL studies have also focused on documenting the well-being and conditions of living of those with chronic medical conditions and disabilities (9–21). This forward momentum within the health care arena has been deterred little by criticism and warnings about the uses and misuses of QOL data (22).

In the geometrically expanding quality-of-life literature, it is often noted that researchers cannot agree upon what "quality of life" means, or how it ought to be measured (6, 23, 24). Indeed, quality of life appears to have as many definitions (implicit or explicit) as the number of publications that have incorporated this construct. This uncontrolled growth in definitions parallels the development of a profusion of QOL measurement tools, which have been regularly catalogued and appraised (25, 26). The QOL tools developed or adopted for use with individuals with disabilities and recipients of medical services include the SF-36 Health Survey (27), the Sickness Impact Profile (28), the Reintegration to Normal Living Index (29), the Community Integration Questionnaire

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(30, 31), the Barthel Index (32), plus hundreds of others (25). As will be discussed below, these tools vary not only in terms of their definitions of QOL (i.e., what the "yardstick" looks like), but also in terms of how and where the "yardstick" is used (i.e., the data source relied upon in assessing QOL). Complexity is added to this definitional and operational chaos by those who see quality of life as unquantifiable and better approached through qualitative study (33).

Thus, as a focus of measurement within health care, QOL remains unfocused, which has resulted in a largely failed mission: We have instances of excellent studies describing QOL within specific groups of people in defined situations, but a cumulative picture of how the well-being of medical recipients is affected by treatment is not being developed. Nor have we developed compelling and coherent profiles of QOL within populations of individuals with varying chronic conditions and disabilities. We have instead a ragged patchwork of results. Although researchers who desire to explore the wider implications of medical interventions by including measures of QOL are to be applauded, inadequate attention to definitional issues has resulted in these authors "talking past each other."

Within this "Tower of Babel," many problems have converged. First, as noted, little agreement has been reached on the definition of QOL. Second, many studies are carried out with no thought given to the definitional distinctions incorporated into the QOL tools adopted or for their implications for the research questions being pursued. And, third, a variety of methodological (rather than definitional) problems weaken the applicability and generalizability of results. For example, too many researchers under-identify the respective samples studied, so that in the end we have very little understanding of whose life quality is being delineated. These methodological issues are beyond the scope of this paper. Instead, our goal is to clarify the definitional choices that affect measurement of QOL within medical research. How do the characteristics of measurement tools we adopt affect our results? Each tool carries with it a specific focus, intrinsic values, level of sensitivity, breadth of view and range of utility. The implicit concepts and models underlying measurement approaches need to be clearly explicated prior to adoption of any particular yardstick.

The basic premise of this article is that measurement of QOL always incorporates value judgments. Such judgments may be implicit or explicit, made by the insider (i.e., the person being measured) or by an outsider, but are always intrinsic to QOL measurement. For example, on the one hand, the insider may be asked explicitly to rate (i.e., place value on) his or her "satisfaction," "well-being" or "quality of life" since Treatment X. Or, on the other hand, the researcher (an outsider) may insert his or her own value judgment and conclude that "their QOL is lower, as most study participants experienced higher levels of depression after onset of disability compared to levels in non-disabled controls."

We suggest that the key question in QOL research is: Whose values are being tapped? We also suggest that the reason QOL is important to measure is that it is the primary means of inserting the insider's values into measurement of health benefits. From the insider's perspective, it is the primary means of becoming empowered within the measurement paradigm. If values other than those of the insider are incorporated into a study, the results speak to the questions of "gains," "societal benefits" or "change," but not QOL. Such research on the benefits of and changes associated with medical treatment are clearly important, but the point here is that they should not be mislabelled as QOL studies.

In exploring approaches to QOL measurement, we will first analyze the two questions underlying such measurement: (a) What parts or elements of life are incorporated into measurement? In the model of life that underlies measurement, what components are deemed relevant to measurement, where is QOL specifically located among them, and how do life elements outside QOL relate to QOL? (b) How is the "quality" of these elements determined? In other words, how does evaluation of life get inserted into measurement, and whose values are adopted? Based upon this analysis, we will then recommend approaches for measuring QOL, ending with a brief discussion of how such recommendations are affected by the purposes to which QOL measures are to be put.

Models Underlying QOL Measurement

Although various QOL measures differ widely, each embodies an operational definition of what QOL is. The measure includes only those aspects and domains of life viewed as relevant to and affecting QOL and excludes those which are not. Models of life underlying QOL measurement can be characterized in terms of the domains/elements included and the structural relationships between those domains. Thirdly, models differ in terms of where within these structured domains QOL is located.

QOL Models: Domains and Elements

QOL models differ, firstly, in the breadth of content areas or domains incorporated. At one end of the continuum are studies of QOL that adopt single variables as indicators of QOL, such as measures of depression or work status. Many tools measuring HRQOL focus also on a relatively narrow swath of the person's lifespace, with the effects of illness, pathology and impairment at the center of the model. The consequences of illness or impairment are highlighted, as with a narrow beam of a flashlight. Thus, measures of handicap, adhering to the long-standing International Classification of Impairments, Disability and Handicap (ICIDH) definition (34), are sometimes used as indicators of QOL. The typical ICIDH-based model states that pathology affects impairment, in turn affecting disability, and in turn handicap. Contextual elements—beyond the initiating pathological event—often are included in ICIDH-based (and other chronic-disease) models; however, their role is clearly secondary (35). As Minaire (36) suggests, these models focus on the social aspects of illness: Illness is the lens through which life is viewed. Chubon (37) argues against the use of many health- and disability-relevant QOL measures because of the narrow focus they adopt.

In measures emerging from social science traditions, a broader view of life is often taken. The impact of pathology is typically acknowledged but is not the central issue, and it is interwoven with other, more broadly defined extra- and intraperson variables. For example, Felce (38) suggests six QOL domains, with no less than five subdomains in each.

The ICIDH definitions of impairment, disability and handicap are currently being revised (39) after being in place since 1980. In the system being tested, the focus of attention is being placed on impairment, activity and participation, thus focusing more fully on functioning within a broad social context. When the revisions become available, broader views of life may become more frequently incorporated into QOL studies within health care research as measures are developed and adopted to reflect the revised ICIDH view.

QOL models also differ in the assumed valence applied to the elements within the domains. In other words, life after onset of disease or trauma may be viewed within some models solely in terms of negative consequences (e.g., symptoms, problems, disability, handicap). Alternatively, a neutral stance may be taken, in which assessment focuses on functioning and assumes that dysfunction neither monopolizes life nor dominates the picture to be drawn of QOL. The difference is exemplified by the thrust of what is typically asked in assessing the person's life: Does the assessment tool ask about problems (thereby taking a negatively valenced view) or does it ask, for example, about the frequency of events such as "using transportation" (a neutral question allowing a range of responses that may indicate a problem for some individuals but a strength for others)?

The predominance of negative views of life after onset of illness or disability is illustrated by Ziebland and her colleagues (40). They posit four models of disability that underlie the items comprising HRQOL assessment tools. Items which, when summed, measure the person's degree of disability, may be couched in terms of a tacit model of total disqualification (e.g., "unable to walk?"), subjective distress (e.g., "trouble bending or lifting?"), comparative limitations (e.g., "more mistakes than usual?") or dependence on other persons or devices (e.g., "need help to walk?"). They suggest that the measured disability level of any individual will vary across HRQOL instruments as a function of the tacit models used in framing items within the respective questionnaires. What "goes without saying" is that a sole focus on disability guarantees a negative view of the QOL of the person with the disability or chronic illness.

A neutrally valenced model encourages a view of the person as more than his or her disability (41), where ability and strengths can be delineated to form a more complete sense of the person's QOL. For example, for studying the QOL of older persons, Raphael and his colleagues (42) generated a measurement approach focusing on three domains: being, belonging and becoming. Further, as Rowe and Kahn (43) suggest with respect to studies of aging, where negatively valenced views are typical, shifting the emphasis from studying "usual" to studying "successful" aging encourages us to seek the factors in the person and environment that promote success.

The newly emerging ICIDH brings with it a less negatively valenced approach than in the past (39). The original version focused on the consequences of pathology in the individual, defining these solely in negative terms (impairments, disabilities and handicaps). This negatively valenced model was widely adopted after the ICIDH's introduction in 1980 (34), despite the burgeoning at that time of measures adopting multidimensional, neutral views of functioning with a disability (44, 45). Again, perhaps when the new ICIDH is introduced, QOL measures will take a broader view of living life with a disability, and one that is less negatively valenced.

Finally, the content incorporated into QOL models differs in terms of the specificity of the items. Thus, some models adopt broadly defined constructs as items for analysis (e.g., "overall goodness of life," "overall mood") or combine specific items into broad, construct-oriented scores (e.g., "work handicap"). Other models are noted for their concreteness and specificity (e.g., "satisfaction with leisure activities," "number of different people visited in the past month"). For example, in their research, based on an ICIDH-type model predicting QOL of individuals with traumatic brain injury (TBI) living in the community, Heinemann and Whiteneck (10) found that QOL was most strongly associated with the broad concepts of social and work handicaps, accounting for 13% of the variance. In contrast, Granger and colleagues (46), studying a sample of 22 young people with TBI, predicted 80% of the variance in general life satisfaction using three relatively specific variables: access to transportation, depression level and problem-solving ability.

QOL Models: Structure

Models underlying measurement of QOL also vary in the structural relationships posited between domains. In the simplest unidimensional models, QOL is located in a single "place" (e.g., "QOL is equivalent to the person's level of depression") and no relationships with other life elements are incorporated into the model. More often, QOL models go beyond such simplicity in one of two ways: Some posit multidimensional components that together comprise QOL (e.g., "QOL is constituted by work status, degree of social contact and health status"). Others may include a variety of factors that together predict QOL, but which themselves are considered external to and not components of QOL (47) (e.g., "QOL—however measured—is predicted by work, social contacts and health"). Often a combined approach is adopted: multidimensionally defined QOL predicted by a variety of external factors.

Multidimensional models vary in terms of the types of linkages specified between components of the model, varying along a continuum of the degree to which hypotheses about relationships between variables as well as causal links are incorporated into the model. Residing at one end of the continuum are descriptive multidimensional models. In such models, multiple domains of the individual's lifespace are viewed as comprising QOL, but relationships between domains and elements remain unspecified. For example, Dennis and her colleagues (23) suggest that QOL is a function of three sets of factors: those factors unique to the individual, those unique to the individual's culture and those common to all people. These domains are posited, but neither how they interrelate nor how they "produce" QOL is specified.

At the other extreme of this continuum are models that posit specific causal, explanatory linkages between components of QOL. For example, Ormel and his colleagues (24) propose a social production function framework underlying QOL, through which they causally link health to quality of life measures. Within their view, people work to maintain their psychological well-being (i.e., QOL) by trying to optimize achievement of universal needs (i.e., physical and social well-being) via six instrumental goals (i.e., optimal level of arousal, pleasant environment, absence of physiological needs, control over scarce resources, behavioral confirmation and affection). Addressing these goals occurs within the context of the individual's resources, instrumental activities and endowments. Ill health or impairment typically reduces the individual's repertoire of instrumental activities, so that instrumental goals as well as physical and social well-being are threatened. The individual may shift activities and the use of resources to get his or her needs met. If substitutability is limited, QOL will decrease.

At the midpoint of the continuum are correlational or predictive models. These models not only posit diverse domains that "capture" QOL but also pinpoint linkages (correlational or predictive) between domains. In other words, models of this type provide more than a list of domains found in descriptive models, but less than an explanation of how domains relate to each other, which is associated with truly causal models.

It should be noted that predictive and causal models may posit non-linear relationships between elements or domains and QOL (24), including what Batterham and his colleagues refer to as threshold variables (48). Thus, for example, Lindstrom and Köhler (49), in comparing QOL of adolescents with disabilities to those without disabilities, analyzed the percent of these youths' families achieving a set threshold on each of several variables (external conditions, interpersonal functioning and psychological well-being).

It should also be noted that through the logic of the model's predictive or causal structure, key domains and elements of the model may play a strong role in dictating the remaining elements.

For example, medical models that underlie measures of health-related QOL (36, 50) often "begin" with pathology. They suggest that HRQOL is produced as a function of pathology interacting with a variety of elements within the individual and his or her environment. Thus, Wilson and Cleary (51) tie QOL to health within a framework of complex hierarchical effects. Health-related QOL within their model is directly affected by the individual's values and preferences, general health perceptions, and social and psychological supports, as well as by "nonmedical factors." Pathology, within this model, is the prime mover, but only directly affects QOL through general health perceptions. However, pathology dictates many of the domains of interest that are incorporated into the model and is the organizing principle within the model.

QOL Models: Location of QOL

Models vary in terms of where within the structured domains one looks to find the "life," the "quality" of which is being evaluated. Models differ at the grossest level in terms of whether QOL is located solely within the judgment of the insider or, instead, outside that judgment, or whether QOL is a combination of the insider's judgment and external variables. Thus, QOL has been conceptualized as solely the insider's judgment of the "goodness" of his or her life (whether cognitively and/or emotionally conceived) (47, 52). Within this view, the QOL judgment depends on the insider's values and how much weight is given by the person to each element of life that potentially affects "goodness." The insider may incorporate every potential domain of life in arriving at a judgment or may include very few. He or she may explicitly review life's elements or may simply provide a "gut reaction." No matter how compelling any factor may seem to an outsider (such as severe depression or a fire that destroys an individual's possessions), the insider's QOL judgment may or may not be affected by these externally defined "catastrophes," depending on the insider's valuation of them. Thus, in this approach, "life" is outside the insider's judgment, but QOL resides totally within.

In contrast, models aimed at documenting QOL at the level of the community (53) typically have focused on factors fully external to the individual (e.g., measures of housing conditions, crime, pollution, quality of schools). In other models, factors "attached" to the person, but external to his or her judgment of the goodness of these factors, comprise QOL, including measures of the individual's emotional well-being, statuses, patterns of activity engagement and/or time (54–57) (e.g., level of depression, work status, socializing with friends). In these models, QOL is located fully outside the insider's judgment and, in fact, is located in the judgments of outsiders; this is discussed more fully below.

Some measurement systems define QOL as a combination of the individual's internal evaluation of life's "goodness" and external conditions (58). For example, Felce (38) defines QOL as a function of objective life conditions and personal satisfaction with those conditions, both of which are weighted by the individual in terms of his or her personal values and aspirations. However, all too often the model does not make the locus of QOL explicit (i.e., whether QOL resides both inside and outside the individual, or whether QOL is fully an internal judgment and the external factors included in measurement are merely predictors of QOL).

With models placing the person's internal judgment of "goodness" at the center of QOL, debate has focused on whether QOL should be assessed by seeking a single judgment of this experience or by separately evaluating several areas of the individual's view of life, such as family life, friendships and work (24, 59, 60) (i.e., is the internal judgment of QOL unidimensional or multidimensional? And, do we gain in our knowledge of QOL if we ask the insider to make the basis of his or her evaluation explicit and multidimensional?).

Values: Insiders vs. Outsiders

QOL measurement varies not only in the model adopted but also, and most importantly, in terms of the values that hold sway during the evaluative process that defines QOL assessment. Whose values are acknowledged: those of the insider or those of an outsider (e.g., family member, physician, researcher)? A variety of avenues are available within QOL measurement to give preferential place to the insider or to one or more outsiders; this preferential place carries with it the power of being heard. This is done, first, in assigning responsibility for assessing the "goodness" of an individual's (or group's) QOL to either the insider or outsider. Second, power also resides in the act of deciding the importance or relevance of domains of life that potentially affect QOL. Thus, for example, power is given, on the one hand, to the evaluator of the "goodness" of the insider's recreational life, and, on the other, to the person who decides if this aspect of life will be evaluated at all (i.e., is it one of the domains included in the QOL assessment?) and if so, how important it is to the focal person (i.e., the respondent).

The issue of whose values are given sway is highly correlated with, but potentially independent of, where QOL is located. For example, if QOL is located within the insider's judgment, it would seem logical to ask the insider to evaluate his or her own QOL. However, other approaches are conceivable. For example, QOL defined as the insider's judgment might be assessed by asking family members to judge the insider's sense of well-being, especially if the insider's cognitive or emotional functioning is in question. One can also imagine the internal experience of QOL being measured "objectively," such as by using serotonin levels or other physiological measures as indicators of the insider's experience of overall well-being.

A critical point here is that various sources provide different views of the target individual's life, any one of which may be useful. The problem occurs only when these views become substitutes for and replace the insider's view. Thus, when a measurement system adopts one particular perspective, the implication is that that source has the authority of truth, because it is the evaluator's values that are incorporated into the assessment. In this vein, Minaire (36) argues that "quality of life" should only be applied to subjective assessments by insiders. He views QOL as "belonging" to the person, in effect defining or "making" the person who she or he is. Although this debate has often been couched in terms of subjective vs. objective assessment, it is really a matter of whose values holds sway: the insider's or the outsider's.

Clearly, when an outsider is the subjective evaluator of the insider's QOL, the outsider's values are given predominance. This is also the case when researchers replace the insider's values with their own assumptions about societal values. For example, if "better" QOL within a study is defined as a function of income level and education, the implicit value typically adopted is that higher levels of attainment in these areas are correlated directly with higher levels of QOL. However, for many individuals, their achieving up to a threshold in these areas contributes to their experience of QOL, but achievement beyond that point has no effect. In this case, their values are not congruent with the value assumptions of the QOL model.

Sometimes, societal values are incorporated into the QOL assessment through the use of normative data from the general population or from subgroups, such as other disability or illness groups. For example, the QOL of a group of people with disabilities, when compared to a non-disabled group, may be judged lower by the researcher because it evidences more depression than is typical in the control group. This judgment does not flow intrinsically from these data, but instead from the societal values being adopted by the researcher.

Some have criticized insider assessment of QOL, because these measures may be less a reflection of the person's "real" QOL than the person's psychological adjustment to disability. In other words, the insider's assessment of his or her satisfaction or well-being is viewed as being an unreliable indicator of the "real" conditions, actions and events that affect or comprise QOL. So, for example, in some studies of QOL, the smaller-than-expected differences found in QOL judgments between people with disabilities and those without have been viewed as underestimates, as the individual with a disability is assumed to be denying or minimizing his or her true feelings (61). In one study, people with disabilities rated health and mobility as "less important" in their lives than did a non-disabled comparison group; the authors suggested that this resulted from a selective de-emphasis of those functions affected most by disability, due to adjustment and habituation processes (9).

The issue of subtly shifting judgments of QOL is not problematic, however, to those who view "real" QOL as residing within the insider's judgment. QOL assessments that shift to fit the person's internal dynamics and values are expected (62), even if they do not "fit" shifts in external realities, such as changes in work status, mobility or the like. Complementary subjective and objective measures—what we would call a combination of insider and outsider assessments—have been recommended to address this issue (48, 63). However, we believe that this simply sidesteps the question of whose values hold sway. We would argue instead that when the insider's assessment of QOL and objective QOL data (or an outsider's value judgment) correlate poorly, two aspects of life are being measured: true QOL and external predictors, which simply follow different rules of cause and effect.

To this point in the discussion of how insider vs. outsider values are incorporated into QOL assessment, we have focused primarily on power that flows from being the evaluator of the "goodness" of the insider's life. Empowerment also resides in evaluating the relevance to QOL of items and domains. Typically, the domains and specific items within QOL measures are generated (by the researcher) through deductive procedures; further, all items are deemed (by the researcher) equally relevant to all respondents. However, this dominance of the researcher's values has been challenged in two ways. First, inductive approaches have been used to generate items/domains felt to be relevant by representatives of a population. Thus, using an inductive approach, Flanagan (59, 64) analyzed 6,500 critical incidents obtained from 3,000 study participants to develop his 15-scale QOL measure. Similarly, individuals have participated in focus groups, surveys and interviews to generate the items that comprise domains they view as relevant to QOL measurement (65 – 68). In diverse ways, inductive methods have been used to develop standard lists of items and domains that reflect the views of insiders.

A second way in which the values of the insider have been acknowledged is by asking the insiders to rate the relevance of components of a standard measure (in addition to their degree of satisfaction with respect to each element) (9, 59, 64). For example, Lankhorst and colleagues (69, 70) asked individuals with spinal cord injury and rheumatoid arthritis to rate their abilities on 39 items (primarily activities, such as climbing stairs and travel). They then asked respondents to rate the impact of each item on their lives. The final score reflected the sum of each item's ability rating weighted by its importance to the individual.

In sum, in the approaches to QOL measurement that are most empowering, individuals dictate the elements that are included, how important each is to their lives and how well they are doing with respect to each element (71, 72). We join many in the field who argue for the importance of adopting measures that fully incorporate the consumer's voice in defining how domains and elements vary in importance for each target individual (5, 6, 63, 73), and who in general urge that the insider's perspectives be sought (74).

Measurement of Quality of Life

The characteristics of QOL models and measurement that we have outlined can be applied in developing recommended approaches to measurement:

- QOL has been located either within the insider's judgment of the "goodness" of his or her life or outside this judgment.

- The insider's and/or outsider's values may hold sway in deciding which aspects of life are relevant to QOL and the voice that will be heard in rating the degree of "goodness" of life.

- QOL models incorporate domains of items varying in breadth and specificity; they take either a negative or neutral view of functioning.

- QOL models vary in their complexity, type of linkage between components and their inclusion (or not) of both the insider's judgment and external predictors of QOL.

Given these distinctions, what recommendations can be made for measurement of QOL? First, a sine qua non of QOL measurement is incorporation of the insider's values, both in terms of ratings of "goodness" and ratings of the relevance of items and domains. Thus, the essential measures within a QOL study are those that emerge from within the insider's judgment and that fully express what is relevant to his or her judgment. Secondary measures (if any) can be obtained from any other source and express the values of others; they may be used simply to supplement or complement the judgment provided by the insider or to predict the essential QOL data. The corollary is that if the essential (insider-driven) data do not exist, the study is of something other than QOL.

Essential QOL measures can be obtained in at least three ways, reflecting unidimensional vs. multidimensional views of QOL:

- Single, standard items have been developed to tap the insider's overall rating of the "goodness" of life (1, 75). Such items assume that the insider implicitly or explicitly considers and appropriately weights each component of life relevant to him or her (e.g., work, family relationships, significant other, mood) in reaching a single judgment of the overall "goodness" of his or her life. The shortcoming of this approach is that it does not reveal the elements that the insider is considering when evaluating QOL. Researchers can analyze external predictors of this QOL judgment, but not the multidimensional value judgments that contribute to the overall judgment.

- The researcher can ask the insider to generate an individualized list of aspects of life he or she considers relevant to the QOL judgment (65). In this approach, the insider's task is to then rate each life component both in terms of the degree of its relevance to his or her QOL and its "goodness" within his or her life. The drawback of this method is the lack of comparability of items across participants in a study.

Also, participants may vary widely in their ability to generate the full range of items that significantly affect their QOL. An individual with a toothache comes to mind: momentary pains and pleasures may take over in generating a list of "what's important" at the time of participation in the study.

- To avoid the limitations noted above, the researcher can develop a list of life components (inductively or deductively) or adopt an existing list, such as that developed by Flanagan (59, 64). The insider's task is then to rate each item in terms of relevance and "goodness." In adopting such a list, the researcher also needs to include the opportunity for the insider to add one or more components not included on the standard list, to insure that all life areas relevant to the individual's judgment of QOL are available. Using a combination of Flanagan's list and a single-item measure of QOL, Brown and Vandergoot (75) recently explored how internal values predict the overall judgment of QOL in samples of individuals with TBI and with spinal cord injury.

Two additional attributes are necessary in obtaining essential measures of QOL. First, a broad range of life elements must be included in the evaluative task. Narrow measures, such as those tapping vocational outcome, mood or health status, by definition do not "capture" the intrinsic breadth of "life." Nothing but conceptual confusion arises from (for example) operationalizing QOL as "level of depression" or any other single variable or narrow band of variables. A welcome trend is the specific labelling of health-related QOL, differentiating it from broader-based views of QOL.

Second, the evaluative task must be a neutral in considering the elements of life. Because the focus is on "life," not on problems or consequences of pathology or the like, the "yardstick" should provide as much opportunity to reflect on what is good about life as on what is bad. The measuring tool, in other words, should be unbiased, designed to permit measurement of both negative and positive elements of life. Assessing problems, symptoms, disability, depression and the like may be important, but their summation does not reveal the quality of a person's life.

In sum, we suggest that QOL can only be measured by tapping the insider's values and by insuring that a broad, neutrally valenced review of life is incorporated into the rating task. Beyond this minimum, two additional qualities recommend themselves in QOL measurement:

- Adoption of a multidimensional model that causally links the external world to the insider's judgment. In this way, QOL research can explore the factors that most strongly affect the insider's experience of life. In addition, it is clear that models that provide explanatory linkages between elements of the model are more useful in the long run, particularly in terms of generating testable hypotheses.

- Incorporation into the model of content that has high specificity. Too often, broad constructs (e.g., "work handicap") are achieved by summing items that respectively may have very different effects on the QOL judgment. When they are deconstructed, their contribution can be more easily revealed. However, pilot studies are needed to determine which of the hundreds of possible specific life elements correlate with QOL, and among which groups.

The Research Purposes to Which QOL Measures Are Applied

Finally, how does the purpose that the QOL instrument is to serve affect the development or adoption of one system rather than another? In addition to their use in clinical practice (71, 76, 77), which is beyond the scope of this paper, QOL data are used in research for three basic purposes.

First, much of the attention being paid to QOL measurement follows from its use to assess the effects or outcomes of health interventions, either as the sole evaluative measure or, more typically, as one component in a total package, including measures of impairment, disability and/or handicap (6, 78). When used in outcome studies, QOL assessment must be based on an underlying model that includes the most probable loci of the effects of the intervention in the target's life. For example, if one is comparing the QOL of individuals who received Treatment X with that of individuals who received Treatment Y, the model of QOL adopted should be one that contains the domains most likely to be affected by these treatments, as well as elements/predictors expected to moderate the effects of treatments. More specifically, outcome studies benefit from the adoption of predictive or causal models of QOL, which provides a basis for linking one event (e.g., provision of services) to a subsequent event (i.e., any outcome, including QOL).

In outcome research focusing on QOL within the context of health care, with rare exception a medical model is adopted, in which the insider's health and medical interventions play major roles.

The focus is relatively narrow: how illness affects QOL and how this can be alleviated with drugs, surgical techniques and the like. Lehman (79) argues that a broader QOL framework is more appropriate for assessing QOL in individuals with chronic or disabling conditions, as a broader view will "account not only for direct health outcomes but also for the potential social and economic effects of medical disability."

A second research purpose for which QOL data are obtained is to describe populations and subgroups (80). For example, is QOL different for people with disabilities living in rural areas compared to suburban or urban dwellers? How does HRQOL vary geographically, across states or countries? In studies of individuals with disabilities that address the question of how subgroups differ, QOL data from one group may be compared to data from groups with other types of disability or to data from groups of people without disabilities, to provide both a contextual base for broadening understanding and implicit societal values for evaluating the respective groups (11 – 13).

A third (related) purpose for which QOL data are obtained is to provide a basis for developing policy. If one wants to develop policy, for example, regarding the need for nursing homes, a medical model may be appropriate. If one wants to know what a subgroup living in the community needs in the broadest sense, a less health-driven approach is warranted (41). In either case, selecting a neutrally valenced, broadly focused approach, including complex predictors of QOL, encourages the documentation of areas of strength, which may provide useful insights into variables that support success.

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Acute Management of Traumatic Cervical Spinal Cord Injuries

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Abstract

Successful outcome from a traumatic cervical spinal cord injury (SCI) depends heavily upon the quality of the acute care rendered to the affected individual. In recent years, there have been significant advances in the acute management of SCI. We discuss current management strategies in the areas of prehospital care and transport, emergency room management, surgical considerations and pharmacotherapy. **Key Words:** Tetraplegia, stabilization, decompression, methylprednisolone.

SPINAL CORD INJURY (SCI) is a catastrophic event and one of the most common causes of severe disability and death following trauma (1). Approximately 10,000 acute spinal cord injuries occur in the United States each year. Tetraplegia, defined as loss of sensorimotor function as a result of an injury to the cervical spinal cord, accounts for approximately 55% of all SCIs (2–4). The Edwin Smith Surgical Papyrus of Egypt described SCI five thousand years ago as "ailments not to be treated" due to the poor prognosis (5). Fortunately, this has changed and a recent study of patients with traumatic SCI resulting in tetraplegia showed that 85% of these patients were alive 5 years after their injury (6). Though much has changed over the last five thousand years, to date no one has discovered a regenerative process to repair the traumatically injured spinal cord in humans. As a result, the outcome of the injured individual is often determined by the acute management of the SCI. Over the past two decades, great improvements have been made in the area of prehospital emergency care and the initial medical, surgical, and pharmacological management of the spinal-cord-injured person (7).

Prehospital Management

Early management of the cervical-spinal-cord-injured patient begins at the scene of the accident. It has been estimated that 3–25% of spinal cord injuries occur after the initial insult, either during transit or early in the course of treatment (8). Over the last 20 years, there has been a dramatic improvement in the neurologic status of SCI victims arriving in the emergency room. During the 1970s, the majority of patients arrived with complete neurological lesions. During the 1980s, however, the majority of spinal-cord-injured individuals arrived in the emergency room with incomplete lesions (9). This change in neurological status is extremely important, in that patients with incomplete injuries have a far better prognosis for neurological recovery than those with complete injuries. This drastic improvement in neurological status seen in the emergency room has been attributed to the development of the Emergency Medical Services (EMS) system.

An EMS system is an integrated and organized emergency response system. It consists of many

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components, including trained responders (i.e., paramedics) who utilize appropriate extrication techniques, and who are trained in basic and advanced trauma life support. It also includes emergency transportation with communication linkages between a central coordinating center and a trauma center (10). Therefore, it is clear that the management of acute cervical SCI begins with prehospital care by EMS at the scene of the accident.

Prehospital care consists of five phases: evaluation, resuscitation, immobilization, extrication and transportation (11). The evaluation is made up of two parts: the primary and secondary surveys. The primary survey consists of evaluation of the airways, breathing and the circulation (the "ABCs"). The secondary survey consists of a more thorough evaluation, from head to toe, of the injured person. During the evaluation it is important to consider the possibility of an SCI. Any victim who is unconscious is considered to have an SCI until proven otherwise. A conscious accident victim may complain of neck or back pain, or palpable tenderness in those areas. There may be signs of muscle weakness, paralysis, or altered sensation in the trunk or extremities. If these signs are not present, it is important to ask the patient if they ever were noted, even if only temporarily. Deep tendon reflexes may be lost. There may be signs of incontinence or urinary retention due to loss of bowel and bladder function. Priapism may be present, or there may be a loss of anal sphincter tone. Signs may be subtle, such as increased skin warmth and flushing due to loss of sympathetic vascular tone below the level of the injury. There may be superficial signs such as abrasions, lacerations or deformities of the spine, neck, or head regions. Injuries to other areas such as the head may mask an SCI. In addition, altered states of consciousness due to alcohol or drug use may also mask an SCI.

Resuscitation begins during the evaluation and primary survey. The neck should never be moved out of a neutral position in order to establish an airway in any patient suspected of having a spinal injury. Any patient with a suspected SCI should be given supplemental oxygen during transport to the hospital. In the alert patient with a C5 lesion or lower, oxygen can be given by nasal cannula or face mask. In the obtunded patient, oxygenation may be facilitated with a chin lift maneuver and insertion of an oropharyngeal airway. However, if adequate oxygenation cannot be maintained or established due to respiratory arrest, the victim must be intubated. The esophageal obturator airway (EOA) (12) or blind nasotracheal intubation are methods of choice, because either can be accomplished without hyperextending the neck. Although endotracheal intubation provides better oxygenation, the EOA will provide adequate ventilation during transport. If endotracheal intubation is necessary, an assistant should stabilize the neck during the procedure.

It is of critical importance to reestablish circulation to neural structures if there is to be any recovery of neurological function. External cardiac massage must be started if necessary. Any active bleeding should be attended to. Bleeding from the neck or spinal area should be controlled by direct localized pressure. Circumferential pressure dressings should not be used. There is some controversy surrounding the establishment of intravenous lines at the scene of the accident. Standard procedure consists of the insertion of a large-bore intravenous line with infusion of Ringer's lactate in all SCI patients. Others, however, believe that if rapid evacuation to a trauma center is possible, delaying transport to start intravenous lines at the scene of the accident is not beneficial.

The cervical SCI patient may present with either neurogenic or hemorrhagic shock. Neurogenic shock is the result of a spinal cord injury at or above the fourth thoracic vertebra. Such injuries result in the loss of sympathetic nervous system control of peripheral vascular tone. This leads to the pooling of blood in the extremities and reduced central venous return, resulting in compromised cardiovascular function. There is an associated bradycardia due to the loss of sympathetic innervation to the heart and unopposed parasympathetic tone. Both hemorrhagic and neurogenic shock present with systolic blood pressure of approximately 70 mm Hg or lower. However, neurogenic shock presents with bradycardia and a slow, regular pulse, while hemorrhagic shock presents with tachycardia and a rapid, irregular pulse. The situation may be complicated by a combination of both types of shock. The quickest and easiest treatment for either type of shock is placement of the patient in the Trendelenburg position. This will help decrease the lower extremity pooling of blood and increase central return. The specific treatment for neurogenic bradycardia is the administration of 0.4 mg of IV atropine, or IV dopamine hydrochloride via low dose infusion. However, this is only a temporary measure. Caution should be used in delivering fluids to patients in neurogenic shock. In these patients, the problem lies not in the volume of blood loss, as is the case in hemorrhagic shock, but in its distribution. Large increases in volume may cause these patients to develop heart failure. While the use of MAST pants (Military Anti-Shock Trousers) has been shown to benefit patients in hemorrhagic shock by collapsing lower extremity and abdominal vasculature, their role in neurogenic shock has not been established. Special care should be observed when using MAST pants in instances of suspected lumbar or thoracolumbar fractures, as they can aggravate the neurologic injury.

Immobilization of the spinal column and the patient is critical in SCI. Regardless of the posture in which the spinal-cord-injured individual is found following the accident, all patients should be placed in a neutral supine position. The following recommendations for moving a victim with suspected cervical spinal cord injury have been made.

With very gentle traction, with hands locked under the jaw and neck, the patient's head and neck should be placed in alignment with the axis of the body. As long as the neutral position is not surpassed, no further damage to the spinal cord will occur with this maneuver. Traction with weights should never be applied at the accident field because of the danger of over-distraction in cases of severe spinal column disruption, which could result in secondary injury with aggravation of neurological deficit (9).

It has been estimated that as many as 20% of spinal cord injuries involve multiple skeletal levels. As a result, the entire spinal column must be immobilized and splinted from the top of the head to the bottom of the buttocks. The best method of splinting the patient is by using a rigid, straight board. The neck is best immobilized by securing it with a hard collar and sandbags on each side and with tape or Velcro straps tightly over the forehead. The chest should be strapped in lightly so as not to impede breathing. Soft collars should not be used, since they do not sufficiently immobilize the neck to protect against further injury. Philadelphia Collars, while providing better support, also do not provide enough support for some of the more rigorous motion that may be experienced during extrication and transportation. These devices can also give victims a false sense of security. If stressed, they will allow mobility of the neck.

Common sense is the most important factor in extrication and transportation of a patient. No two situations will be the same. With respect to extrication, the status of the patient, accessibility, and any environmental hazards will determine how the situation should be handled. The ultimate goal is to safely remove the patient from the accident scene for transportation to the hospital. A patient's status, injuries and location with respect to a suitable trauma facility will determine the method of transportation (i.e., by land or air).. Although speed is important, the most important factor is getting a patient safely to the emergency room with all systems stabilized, in order to enhance the potential for maximum neurological recovery.

There is some controversy surrounding the type of trauma center best suited for initial treatment of the SCI patient. There are three levels of trauma centers as defined by the Committee on Trauma of the American College of Surgeons (13). Level I centers offer tertiary specialized care for major trauma such as SCI. These centers have 24-hour physician coverage in all specialties and 24-hour operating rooms, laboratories, and intensive care units. Level II centers have similar resources but on a 30-minute response time basis. They are not equipped to handle certain major problems such as SCI. Level III centers are responsible for stabilization, preliminary diagnosis, and preparation for transport of severely injured patients to level I or II centers for better care. The controversy lies in the question of whether the acute-spinal-cord-injured patient should be taken to the nearest hospital, or be transported to the more specialized level I trauma center, even if the distance is greater and it would take more time. Many believe that the acute-spinal-cord-injured person who is stable with regard to vital signs, should be transported past the local hospital to the nearest level I center if the transport time is reasonable (i.e., less than one hour). If the patient is not stable, or the distance is too great, then the patient should be taken to the nearest trauma center for stabilization. Once stable, the patient should then be transported as quickly as possible to a level I tertiary care center.

Emergency Room Management

Upon arrival in the emergency room, the first priority in the management of the traumatic SCI patient is reestablishment of "physiologic homeostasis." It is important to normalize vital signs and blood oxygen levels, and to reestablish as normal a spinal alignment as possible. Much of what is done in the initial stages of emergency room management is a repetition of the EMS management. However, this repetition is critical, since reviews indicate that injuries have been exacerbated and lives lost because of basic errors in emergency room treatment of trauma victims. In addition, it is important to remember that life-threatening wounds, if present, take priority over the SCI.

As with the evaluation at the scene of the injury, the "ABCs" of resuscitation are the first step. It is critical to safely and carefully establish a stable airway and respiratory status in order to maintain optimal oxygenation, and to restore circulation to prevent shock. Cervical SCI often compromises the respiratory status of the patient. This typically results in the loss of thoracic and abdominal musculature, which assists in breathing. As a result, ventilation becomes dependent solely on the diaphragm. Signs of diaphragmatic breathing include minimal or absent chest wall movement, with passive outward and inward movement of the flaccid abdominal wall. A normally functioning diaphragm requires an intact phrenic nerve, which originates from the third, fourth and fifth cervical roots. In high-level cervical injuries, the functioning of the diaphragm is affected to a degree depending on the level of the cervical injury.

Patients exhibiting diaphragmatic compromise require nasotracheal intubation and ventilatory support. Many practitioners advocate prophylactic intubation in higher level tetraplegics even if they are adequately ventilating initially, as they may soon fatigue and require ventilatory assistance as time progresses. There may also be ascending cord swelling, which could compromise respiratory function. If intubation is required, nasotracheal intubation is preferred over orotracheal intubation or tracheostomy. A tracheostomy could limit surgical access to the spine and should only be performed if there is direct injury to the trachea, or if nasotracheal intubation is technically impossible. As stated previously, great care should be taken not to move the neck out of neutral position. In all severely injured trauma patients, a nasogastric tube should be inserted to decompress the stomach and protect the airway from aspirated vomit.

Blood gases should be obtained, to assure that the patient is ventilating well. Optimal oxygenation is a PaO_2 of at least 100 mm Hg and a $PaCO_2$ of less than 45 mm Hg. A PaO_2 less than 70 mm Hg on room air, or a $PaCO_2$ greater than or equal to 45 mm Hg indicates the need for intubation. According to Soderstrom and Brumback (11), aside from removing or preventing mechanical impingement on the cord (bone fragments, foreign bodies, edema), optimal oxygenation is the most important therapy for injured neurological tissue. Ischemia with resultant hypoxia is a major contributing factor to poor outcome in cord injury.

Circulatory support is the next step. Hemorrhaging should be controlled and vascular access via IV catheter should be obtained to allow for the delivery of fluids and to allow for blood studies. The patient should be assessed for shock. In most trauma patients, blood loss is the cause of shock. However, as stated previously, a patient with SCI above the fourth thoracic vertebra often presents with neurogenic shock. Neurogenic shock should be suspected in any spinal-cord-injured patient who presents in shock without evidence of any other injuries, or in a patient who does not respond to adequate fluid resuscitation. In a study by Soderstrom and Ducker (14), 23 of 111 patients with complete SCIs presented in shock. Of these 23, 19 had neurogenic shock. In those patients presenting with a complete lesion, 60 of 190 presented in shock. In these 60, 49 developed neurogenic shock.

After the primary survey has been completed and the patient's respiratory and circulatory status have been secured, a more thorough secondary survey should be performed. A thorough neurological exam should be performed to assess whether an SCI has occurred and if so, to determine the extent of the neurological deficit. Recognizing the need for uniform standards to assess neurological deficit in cases of spinal cord injury, the American Spinal Injury Association (ASIA) created the Standards for Neurological and Functional Classification of Spinal Cord Injury (2). These standards provide guidelines for the systematic examination of the dermatomes and myotomes in order to determine the neurologic level of injury. The ASIA Impairment Scale provides a method to characterize any residual function below the level of the spinal cord injury. The neurologic examination should be repeated frequently, so as to detect any deterioration or improvement in neurological function (15).

It is important to determine whether an SCI is complete or incomplete. As stated previously, an incomplete injury is one where there is preservation of sensory and/or motor function below the level of the injury. This must include the lowest sacral segment. Sacral sensation is defined as sensation at the anal mucocutaneous junction, or deep anal sensation. Sacral motor function is defined by the presence of voluntary contraction of the external anal sphincter. A complete spinal cord injury is one in which there is no sensory or motor function in the lowest sacral segments. Surgical intervention and decompression, which will be discussed later, may be based on the completeness of the neurologic injury.

Radiographic imaging plays a crucial role in the evaluation of patients with cervical spinal cord injuries. Routine radiographs remain the single best initial examination for cervical spine trauma. While computed tomography (CT) is a reliable technique to evaluate cervical spinal injuries, it is not an appropriate screening examination (16). The first spine x-ray that should be done is a cross-table lateral view. Hopefully, this can be done in the emergency room with a portable x-ray machine. The patient should remain on the rigid spine board or, if necessary, be transferred carefully to a CT-compatible x-ray cart. It is important that all seven cervical vertebral bodies be visualized on the x-ray, because fractures and dislocations may be missed if the lower portion of the cervical spine is not included (17). It is critical to remember that an apparently normal lateral x-ray does not rule out the presence of a ligamentous injury. Other views such as anteroposterior, swimmer's, oblique, or open-mouth odontoid views may be required. If the initial cervical x-rays are normal and there is no neurological deficit, then voluntary active flexion/extension lateral x-rays may be helpful in determining stability of the cervical spine. In these instances, a physician must be present during the time of imaging.

In cases of cervical SCI, even if the x-rays appear normal, Green et al. (9) recommend the use of Gardner-Wells tongs and at least 10 lbs of traction. This is done because occasionally muscle spasms in the presence of ligamentous instability can cause delayed column deformity and increased neurological deficit. If fracture or fracture dislocation of the cervical spine is demonstrated on x-ray, Gardner-Wells tongs and traction are applied to reestablish spinal alignment. Muscle relaxants are given to aid in the reduction. Serial x-rays are taken to monitor the success of the reduction. More weight may be added if necessary. Closed reduction of the dislocation is then done under fluoroscopic or x-ray control. If these conservative measures are not effective in reestablishing spinal alignment in patients with cervical spinal injuries, then the patient should be taken immediately to the operating room for open reduction and stabilization. An aggressive approach to reestablishing spinal column alignment is an essential part of reestablishing physiologic homeostasis in patients with SCI.

Once reduction has been achieved, or in those cases where reduction is not successful, the patient is taken for high resolution CT scans. High resolution CT scans can be used to detect spinal cord compression by displaced bone and to determine residual canal size. Metrizamide myelograms to assess spinal cord compression are not necessary if high resolution CT scans are available. CT scans can also be used to better elucidate subluxation, fractures, and subtle signs of ligamentous injuries. Magnetic resonance imaging is not yet a practical test for an acute SCI in the Emergency Department, though it can precisely characterize cord integrity and compression later on.

Once all the historical, physical and neurological examinations have been completed, and radiographic data have been collected, a decision is made on the appropriate treatment course for each patient with cervical SCI. It is at this point that surgical management of the spinal injury is discussed.

Surgical Management

The role of surgical intervention in treatment of traumatic cervical spinal cord injuries is controversial. Ideally, its purpose is to improve neurological function where possible, prevent further neurological damage, and restore spinal stability and alignment quickly (18–19). However, some believe that surgical intervention is not necessary, and even futile in most cases (20–22). Their argument is based on the fact that many studies fail to demonstrate that surgical intervention improves neurological outcome (23–27). Further, spinal alignment and stabilization can often be effectively achieved through conservative, nonoperative means such as postural reduction.

When discussing the surgical treatment of a patient with a traumatic cervical SCI, one must distinguish between skeletal injury and neurological injury. Treatment of skeletal injury to the spinal column is directed at reduction, approximation, and stabilization of the spine. Treatment of neurological injury is directed at relieving spinal cord compression by disrupted bone, disc or ligamentous tissue. Therefore, depending on the extent of the injury, indications for surgery may be either orthopedic, neurosurgical, or both.

The orthopedic management of traumatic cervical injuries focuses on determining whether the spinal column is stable or not. Instability may be thought of as the inability to resist physiological forces. An injury is unstable if the injured segments are capable of shifting position and causing nerve damage during the healing phase. The extent of instability can be determined by assessing the pattern of the fracture (i.e., dislocations, compression fractures, burst fractures), the amount of vertebral displacement, and the types of forces involved in creating the injury (i.e., flexion and compression, flexion and rotation, vertical compression, extension). These factors can be determined by the history of the injury, the physical exam of the patient, and the various imaging techniques mentioned previously.

The presence of neurological deficit in itself is usually indicative of significant spinal column injury, and therefore instability should be suspected in these cases. However, there are many instances when patients with tetraplegia present with a stable spine, so neurological deficit is not an absolute indication of spinal instability. It is important to note that major ligamentous injury often creates spinal instability without fracture. In these cases the spine is not only acutely, but also chronically unstable, and will require more aggressive surgical treatment. For the cervical spine, any vertebral subluxation greater than 3.5 mm or angulation of the vertebrae greater than 11 degrees indicates major ligamentous injury, though there are different criteria defining instability for the occiput-C1 and C1-C2 levels.

The treatment of most patients with stable cervical spinal injuries (e.g., compression fracture) is conservative and nonoperative. Nonoperative treatment of cervical SCI is based on Guttmann's methods of postural reduction. These consist of bed rest with spinal alignment maintained through traction, pillows with sandbags, or a cervical collar. Once pain decreases, the patient resumes activities with a collar for a period of 6 – 12 weeks. The fractured area is periodically evaluated radiographically to ensure that progressive deformity does not develop. If deformity is noted, surgical stabilization is necessary. In addition, any sign of progressive neurologic deficit is an indication for surgical stabilization and possibly decompression.

In the case of unstable spinal injuries, many advocate surgical stabilization, whether a neurologic deficit is present or not. Better spinal alignment is achieved in patients treated surgically. In addition, early surgical stabilization allows for earlier mobilization and rehabilitation of patients. For patients with flexion-distraction injuries, surgical stabilization is also required, because these patients are at risk of progressive spinal column deformity if treated conservatively (36). As mentioned above, surgical stabilization also is required in cases of major ligamentous damage because these cases will result in a chronically unstable spine (36).

Surgical stabilization procedures for the cervical spine consist of anterior and posterior fusions. The type of procedure selected depends on the extent of bone and ligamentous damage. Posterior fusion often is used in those cases of cervical injury where decompression is not required. In unstable injuries also requiring decompression, anterior fusion is preferentially performed. Care must be taken in performing anterior fusion in cases with major posterior ligamentous injury. It has been observed that, in these cases, anterior fusion has led to increased cervical spine instability. This is due to the fact that, during anterior fusion, manipulation of the anterior longitudinal ligament and the anterior portion of the vertebral body disrupts anterior column stability. As a result, if anterior fusion is done in a case with major posterior ligamentous injury, then a separate posterior fusion may be required to stabilize the spine.

Since the advent of the halo vest, many unstable injuries in the cervical spine have been treated nonoperatively by this technique. This method of management is satisfactory as long as the reduction of the fracture can be maintained. Stabilization of subluxations and dislocations can also be managed by means of a halo vest after reduction. After 6 – 12 weeks, the injury is evaluated by flexion and extension views under the supervision of a physician. If the injury is stable, the halo vest can be removed. If it is unstable, an additional month in the halo vest is recommended. If the bodies ultimately fail to fuse, surgical fusion is recommended. The halo vest has fallen out of favor in part because it impedes rehabilitation, especially in the higher level tetraplegic.

Neurological deficits in traumatic cervical SCI are often managed by the neurosurgical team. Following spinal cord injury there may be compression on the spinal cord by bone, disc or ligamentous elements. Cord compression compromises neurological function, so it seems logical that surgical decompression be performed if there is any hope of recovering neurological function (28). However, surgical decompression after traumatic cervical SCI is the subject of much controversy. It is uncertain what effect persistent compression on the cervical spinal cord after a traumatic injury has on neurological outcome. Some believe that maximum damage to the spinal cord occurs at the time of injury, so that surgical decompression after the initial trauma will not improve neurological outcome. Wagner and Chehrazi (27) agree that initial injury to the cervical spinal cord remains the primary determinant of neurological outcome, and severe canal narrowing (>30%) with cord compression thereafter appears to have comparatively little effect. However, it is impossible to state that decompression has no effect on neurological outcome, since there have been no studies using a control group whose spinal canals remained compromised. The opinion of many other physicians on this subject is summarized by Bohlman et al. (1). Even though the initial contusion may have caused most or, in many cases, all of the neurological damage, it is the obligation of the treating physician to free the patient of any pathological process that may continue to contribute to the malfunction of the cord.

Despite the controversy, there is some agreement on surgical decompression. It is generally agreed that surgical decompression with stabilization is indicated in patients with cervical spinal injuries who show signs of progressive neurological deterioration and who have evidence of neural compression. Early surgical decompression with stabilization is also recommended for patients with incomplete injuries who, while they may be neurologically stable, have bone or ligamentous material compressing the spinal cord. Bohlman et al. (1) have reported recovery of neurologic function after anterior decompression in these patients. However, there is no reason for early surgery in patients with incomplete injuries who are showing progressive improvement in neurological function. If there is evidence of significant spinal cord compression, surgery at a later date may be considered when neurological improvement has reached a plateau.

Most studies indicate that patients with complete SCIs do not improve neurologically with decompression. As a result, there is no absolute indication for decompression surgery in these patients. However, there may be relative indications to consider. For example, in cases of cervical SCI with radiographic evidence of nerve root compression, an anterior decompression of the cervical roots may lead to recovery in the function of one motor level that ultimately is extremely important in determining the physical capabilities of a tetraplegic.

In many cases, adequate spinal alignment will prevent the need for operative decompression. However, if satisfactory spinal alignment cannot be achieved, operative reduction and decompression are indicated. There are two surgical decompressive procedures: anterior decompression with fusion, and laminectomy. The selection of a spine decompression procedure depends on the location of the spinal cord compression. Posterior laminectomy for decompression in SCI is rarely indicated. In most cases of traumatic SCI, compression occurs at the anterior aspect of the spinal cord. Laminectomy does not provide adequate decompression. In fact, removal of the posterior part of the spinal column could contribute to further instability and neurologic loss. Instead, anterior decompression is performed to remove disc, bone, and ligamentous tissue that is compressing the spinal cord anteriorly. Studies have shown that anterior decompression with fusion in incomplete SCI gives better results than laminectomy or conservative treatment. Laminectomy may be indicated in those cases in which blood, bone, or ligamentous elements are causing compression posterior to the spinal cord. Once anterior decompression is completed, it is important to assure spinal stability by performing a fusion procedure to prevent any further spinal cord damage.

Pharmacological Management

Prevention of further injury to the spinal cord and reestablishment of "physiologic homeostasis" are the most important goals in the early treatment of traumatic cervical SCI. Until recently, this was achieved solely by the methods described previously: normalization of vital signs, maintenance of sufficient blood oxygen levels and reestablishment of spinal alignment and stabilization. However, recent advances in the understanding of the pathophysiology of SCI have led to the realization that post-traumatic changes occurring locally at the cellular level contribute to further injury of the spinal cord. In fact, so damaging is the secondary injury from these pathophysiological and pathochemical changes, that sensory and motor function initially present after the injury may progressively be lost over the next few hours (29). With this in mind, a great deal of attention has been directed at methods of reducing the secondary injury.

The synthetic glucocorticoid, in the form of methylprednisolone sodium succinate (MPSS), has become standard treatment in an acute SCI. The Second National Acute Spinal Cord Injury Study (NASCIS-2) was a multicenter, randomized, double-blind placebo controlled trial which evaluated the efficacy of MPSS and naloxone, an opiate receptor blocker, in the treatment of traumatic SCI (30). This landmark study found that patients receiving exceptionally high doses of MPSS (intravenous bolus of 30 mg/kg body weight, followed by infusion at 5.4 mg/kg per hour for 23 hours) begun within the first 8 hours of the injury showed improved neurological outcome as compared with those receiving placebo or naloxone. This improvement in motor function and sensation was seen at 6 weeks and at 6 months after injury. Further follow-up showed these neurological improvements continued to be observed one year after injury (31).

NASCIS-2 not only confirmed the role of MPSS in the treatment of traumatic SCI, but it redefined its role in the early stages of the injury. The timing of the first dose of MPSS is crucial. Only those patients receiving the drug within the first 8 hours following their injury showed improved neurological outcomes. In addition, a follow-up study found that patients receiving MPSS more than 8 hours post-injury actually recovered less motor function than those given the placebo. The results from NASCIS-2 also altered attitudes toward complete spinal cord injuries. Conventional wisdom stated that while incomplete spinal cord lesions may recover, complete lesions do not. As a result, many people believed that patients with complete spinal cord lesions would not benefit from treatment with MPSS. NASCIS-2 showed that while patients with incomplete injuries recovered more function than those with complete injuries, both groups benefited from the treatment.

GM-1 ganglioside (monosialotetrahexosyl ganglioside) is another drug that has received a great deal of attention for its potential role in the treatment of SCI. GM-1 is a complex acidic glycolipid found at high levels in the cell membranes of the mammalian central nervous system. It is believed to have neuroprotective and neurofunctional restoration potential (32). The Maryland GM-1 trial was a prospective, randomized placebo-controlled double-blinded clinical trial to evaluate the efficacy of GM-1 in the treatment of traumatic SCI (33). The trial group consisted of 34 patients with major motor deficits. Of this group, 16 received GM-1 and the other 18 received a placebo. The GM-1 group received 100 mg/day IV GM-1 for anywhere from 18 32 days (mean of 25.9 days). The first dose was given within 72 hours (mean of 48.2 hours) postinjury. Both study groups also received 250 mg MPSS IV on admission, followed by 125 mg IV every 6 hours for 72 hours. The researchers found that patients receiving the GM-1 ganglioside showed enhanced neurological recovery after one year. Analysis of individual muscle recoveries revealed that the increased recovery in the GM-1 group was attributable to initially paralyzed muscles regaining useful motor function rather than to paretic muscles gaining more strength. It was also noted that recovery consisted of enhanced motor recovery in the lower extremities rather than solely in the upper extremities. The researchers believed that enhanced recovery in the lower extremities corresponded with improved recovery through the injury site. The results from the Maryland GM-1 trial are promising and may point toward another drug for the treatment of traumatic spinal cord injuries. However, a larger study, combining high dose MPSS with GM-1, has yet to confirm a benefit from this treatment. GM-1 has not yet become an approved agent in the United States for this purpose.

In 1997, the Third National Acute Spinal Cord Injury Study (NASCIS-3) was published (34). The three arms of this study were: (1) 24-hour treatment with methylprednisolone; (2) 48-hour dosing (30 mg/kg bolus followed by 48 hours of a 5.4 mg/kg intravenous infusion); and (3) treatment with tirilizad mesylate, a potent inhibitor of lipid peroxidation (35). The tirilizad was administered by intravenous bolus every 6 hours for 48 hours following a standard 30 mg/kg bolus dose of MPSS. Lipid peroxidation, a destructive chemical reaction known to occur as a component of the secondary injury, is inhibited by both high dose MPSS and tirilizad mesylate, a synthetic glucocorticoid analog.

The study, which enrolled nearly 500 spinal-cord-injured individuals from 15 North American centers, demonstrated equivalent efficacy of the 3 treatments if the initial bolus dose of MPSS was given within 3 hours of the injury. Individuals treated with the 48-hour infusion of MPSS had neurologic outcomes superior to those of the other treatments when the initial steroid dose was given between 3 and 8 hours after injury. Though 48-hour treatment with MPSS was associated with more episodes of sepsis and severe pneumonia than 24-hour treatment or with tirilizad, the authors felt that the small increases in these adverse events should not prevent using a prolonged course of MPSS in individuals treated between 3 and 8 hours after their injury.

It is clear that the ultimate outcome for an individual suffering a cervical SCI is largely determined by the quality of the acute treatment provided. Careful management at the injury scene, efficient transport to the hospital, and skilled, experienced personnel with appropriate knowledge of surgical and pharmacological treatment give the injured person the best chance to make a meaningful neurological and functional recovery, while limiting the acute medical complications.

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Functional Status and Its Uses in Rehabilitation Medicine

ELIZABETH A. EASTWOOD, PH.D.

Abstract

Background: Over the past decade and a half, rehabilitation medicine has developed and implemented standardized measures of functional status. Standardized measures of functional status are important for four reasons: (1) clinicians need them to determine whether interventions produce the expected outcomes; (2) managed care companies use them to decide which rehabilitation services and equipment will be paid for; (3) accreditation bodies such as the Commission on the Accreditation of Rehabilitation Facilities (CARF) require empirical functional status and functional outcome measures; and (4) public policy is moving toward a case-based payment system derived from patient need, and type and severity of impairment.

Methods: Review of the literature.

Conclusions: While researchers, clinicians, managed care, accrediting bodies, and federal regulation have each influenced rehabilitation as conceptualized, measured, and practiced, lack of coordination among these groups has hampered agreement on appropriate tools for functional assessment and outcome. Rehabilitation providers, however, will be increasingly accountable to government regulations and managed care companies. **Key Words:** Functional status, functional outcomes, rehabilitation reimbursement, public policy.

THE GOAL OF MEDICAL REHABILITATION is to restore independent physical functioning to the greatest extent possible. For inpatient rehabilitation settings, the goal is to restore functioning so that the patient may return to the community. In an era of increasing cost constraints, however, many fundamental questions about the organization and delivery of rehabilitation services have arisen. The types of services, the setting in which they are provided, the measuring of service efficacy, and payment are all increasingly scrutinized by patients, providers, payers, and policy makers. This paper gives an overview of some of the key issues in functional status measurement and the role public policy has had in shaping services and measurement of functional outcomes.

Service efficacy and payment for rehabilitation services are central policy issues. In order to determine whether therapeutic interventions have achieved desired outcomes, a variety of functional status measures have been developed. There are several reasons why functional status measures are important: (1) rehabilitation clinicians and researchers have wanted to learn what interventions produce positive functional outcomes; (2) managed care increasingly scrutinizes what treatments are being given and whether the patient has made functional gains; (3) accreditation bodies such as the Commission on the Accreditation of Rehabilitation Facilities (CARF) and the Joint Commission on Accreditation of Health Care Organizations (JCAHO) require that rehabilitation medicine have an empirical system for evaluating program outcomes specific to impairments; and (4) federal regulatory bodies have made increased demands that rehabilitation be put under a case-based payment system rather than the current per diem reimbursement system.

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Clinical Issues

The primary reason functional status is measured is that program administrators and clinicians want to know whether their patients improve. Within clinical disciplines, there have been standard measures of functioning and progress, but no measure existed that summarized a patient's overall functioning or the progress in functioning that might be attributable to treatment. Moreover, clinicians and administrators want to be able to compare the outcomes of their treatment with that of treatment provided by others. This can only be accomplished if each provider consistently uses the same instruments and measures of function.

Early efforts were made in the 1960s to measure functional status, most notably Katz's Activities of Daily Living Index (1) and the Barthel Index (2). Since that time, there have been dozens of functional status measures developed for evaluation of rehabilitation patients. As a result, until the late 1980s, it was difficult to compare outcomes across studies, because different measures were employed. This made it difficult, if not impossible, to make generalizations about patient outcomes at different sites. To rectify the lack of standardization of instruments, the Functional Independence Measure (FIM) was developed in the 1980s by Carl Granger and colleagues (3), supported by the U.S. Department of Education. The FIM was developed by examining 36 existing functional status measures, and then testing and modifying them, until those items were identified that could reliably describe and summarize functional status.

The FIM contains 18 items: 13 items describe motor functioning, and 5 items describe cognitive functioning (Table 1). Each of the items is rated on a ranked number scale of 1–7, where 1 indicates total dependence on others to perform the activity and 7 indicates total independence. The range in total FIM scores is therefore 18–126. The FIM assessment is performed within 72 hours after admission and within 72 hours of discharge. It is conducted by direct observation of actual patient behaviors. In 1997, more than a quarter million FIM reports were submitted from nearly 600 rehabilitation facilities in the United States to the Uniform Data System (UDS) (4). UDS is responsible for collecting data, verifying results, and distributing quarterly and annual reports to rehabilitation facility subscribers.

The UDS provides additional information on patients, to help explain the treatment outcome. These variables include demographic characteristics, pre-rehabilitation living situation, payer, type of impairment, comorbid conditions, whether the patient had to return to acute care for a period of time (an interrupted stay), and overall length of stay (LOS).

The FIM has been shown to be reliable, valid, and internally consistent (5, 6). Its strengths are that it is easy to learn and administer, it is not time-consuming, and it provides the basis for a minimal dataset which adequately describes patient functioning. Physical therapists, occupational therapists, nurses, speech therapists, and recreation therapists may all serve as raters. Its major limitation is that it is only a summary. Moreover, cognitive functioning is represented by only five items, and certain areas of functioning dealing with the ability to return to the community are not represented at all. Finally, the numerical (ranked) nature of the measure places psychometric limitations on the instrument in interpretation of data (7).

Since the FIM is measured on admission and discharge, changes in functional status, and therefore functional outcomes, can be measured. The larger the change between admission and discharge, the greater the restoration of functioning. In addition, one may look at LOS to determine how long it takes to achieve these outcomes. When the change in FIM score from admission to discharge is divided by LOS, a measure of FIM gain per day, sometimes termed the FIM efficiency, is determined.

Managed Care

Managed care companies are providing health care insurance for an increasingly greater number of people. For example, in New York State, 17.7% of the population was covered by managed care in 1992; 27.9% were covered by in 1995. This represents an annual growth rate of 16.2% (8). Since virtually all patients who come to acute medical rehabilitation come from an acute care setting, managed care sets guidelines for what they will and will not pay. Managed care companies already know the patient's medical condition. In their capacity as gatekeepers, they also want to know at what level the patient is functioning, what the goals of rehabilitation will be, the duration of treatment, the discharge plan, and whether there is family support. The managed care companies may limit the types of patients who will be permitted to have rehabilitation and the number of days for which they will pay the institution. In many hospitals, there are trained nurses who regularly work with managed

TABLE 1

FIM™ instrument

Functional Independence Measure

L E V E L S	7 Complete Independence (Timely, Safely) 6 Modified Independence (Device)	**NO HELPER**
	Modified Dependence 5 Supervision (Subject= 100%+) 4 Minimal Assist (Subject = 75%+) 3 Moderate Assist (Subject = 50%+) **Complete Dependence** 2 Maximal Assist (Subject =25%+) 1 Total Assist (Subject = less than 25%)	**HELPER**

Self-Care	**ADMISSION**	**DISCHARGE**	**FOLLOW-UP**
A. Eating	☐	☐	☐
B. Grooming	☐	☐	☐
C. Bathing	☐	☐	☐
D. Dressing - Upper Body	☐	☐	☐
E. Dressing - Lower Body	☐	☐	☐
F. Toileting	☐	☐	☐
Sphincter Control			
G. Bladder Management	☐	☐	☐
H. Bowel Management	☐	☐	☐
Transfers			
I. Bed, Chair, Wheelchair	☐	☐	☐
J. Toilet	☐	☐	☐
K. Tub, Shower	☐	☐	☐
Locomotion			
L. Walk/Wheelchair	☐ ☐ W Walk C Wheelchair B Both	☐ ☐ W Walk C Wheelchair B Both	☐ ☐ W Walk C Wheelchair B Both
M. Stairs	☐	☐	☐
Motor Subtotal Score	☐	☐	☐
Communication			
N. Comprehension	☐ ☐ A Auditory V Visual B Both	☐ ☐ A Auditory V Visual B Both	☐ ☐ A Auditory V Visual B Both
O. Expression	☐ ☐ V Vocal N Nonvocal B Both	☐ ☐ V Vocal N Nonvocal B Both	☐ ☐ V Vocal N Nonvocal B Both
Social Cognition			
P. Social Interaction	☐	☐	☐
Q. Problem Solving	☐	☐	☐
R. Memory	☐	☐	☐
Cognitive Subtotal Score	☐	☐	☐
TOTAL FIM Score	☐	☐	☐

NOTE: Leave no blanks; enter 1 if patient not testable due to risk

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care representatives to negotiate appropriate LOS for patients.

Accreditation Issues

Rehabilitation has its own accrediting body, the Commission on Accreditation of Rehabilitation Facilities (CARF). As a basis for accreditation standards, all inpatient rehabilitation programs must have a program evaluation component that includes standardized functional outcome measures. It is in the accreditation arena that standards have moved increasingly toward ensuring that functional outcomes are measured. CARF standards are more stringent and specific than those generated by public policy and are more rigorous in ensuring that appropriate resources are brought to patient care, with attendant outcomes reliably measured and linked to interventions. In addition, the Joint Commission on Accreditation of Health Care Organizations (JCAHO) reviews medical rehabilitation as part of its survey and accreditation process. In the future, CARF and JCAHO have made an agreement to assess hospital-based rehabilitation centers simultaneously, to avoid duplication of effort.

Regulatory Issues

Current interest in functional status measures is not entirely clinically or academically driven. Much of the impetus for using functional status measures in rehabilitation has its roots in federal legislation which mandated a change in hospital payments by Medicare from a per diem, cost-based rate, to a prospective payment system (PPS), or case-based rate, in 1983 (9). Diagnosis-related groups (DRGs) served to underpin case-based rates of reimbursement, irrespective of the length of stay by the patient. This was intended as a cost containment effort to curb Medicare spending for excessive hospital stays. The modeling procedure used to predict length of stay, a proxy for resource consumption, included diagnoses, procedures, age and gender. These variables, however, were inadequate to explain rehabilitation LOS (10) and rehabilitation was made exempt from PPS in 1982 in the Tax Equity and Fiscal Responsibility Act (TEFRA) (PL97-248). In exempting rehabilitation from PPS, however, Congress set a number of criteria in place which had to be met by rehabilitation facilities to receive Medicare payments. Under TEFRA, payment to qualified hospitals is based on traditional retrospective costs, with a per case payment cap added. Clinically, the most important criterion is that the patient be able to participate in at least three hours per day of physical therapy, occupational therapy, speech/language therapy, and other therapies. However, Congress has repeatedly mandated that a prospective payment system be developed for excluded rehabilitation facilities (11, 12).

To develop a PPS that would adequately explain resource consumption for rehabilitation, experts had long maintained that such a model would include patient functional status and that the specific diagnosis was of little importance. Specifically, the first goal was to accurately and adequately classify patients by level of functioning. This assumes a uniform measure of functional status for all rehabilitation patients. The second goal was to determine the level of impairment from the medical diagnosis. For example, it was necessary to differentiate those patients who survive stroke with little or no residual functional impairment from those who have lifelong disabilities requiring constant care. Third, identifying the level of functioning and the specific impairments would serve to develop a case mix index (a severity of impairment measure). The case mix index, in turn, would indicate the type and intensity of services needed by the patient to restore functioning to the greatest degree possible, thus facilitating a case-based payment system.

Work on development and usage of functional status measures to predict resource consumption began in the 1980s at RAND and the Medical College of Wisconsin (MCW) (13). This early study grappled with conceptualization and implementation of a method to classify rehabilitation patients, just as the work on DRGs had developed a patient classification system. Hence, there was great interest in determining whether a measure of functional status would adequately classify patients. In the RAND/MCW study, only 22% of LOS was explained by functional status and other variables. This early work evaluated functional status by retrospective chart review rather than concurrent, observation-based assessment of patients during a course of rehabilitation therapies.

Primary research on functional status as a basis for a patient classification system has been further developed by Stineman and colleagues at the University of Pennsylvania (14, 15). Stineman's work is derived from the admission FIM as the measure of functional status. At the core of Stineman's work is the conceptualization of mutually exclusive groupings of patients, termed Rehabilitation Impairment Categories (RIC), similar to the major diagnostic categories (MDCs) into which specific DRGs fall. In the most recent model, 92% of all rehabilitation patients were able to be classified into one of the 20 RICs, indicating that the RIC model is able to describe impairments of almost all rehabilitation patients. Table 2 shows the 20 RICs.

The prevalence of patients in impairment groups varies widely. Fig. 1 compares data from the Mount Sinai Hospital to that from the United States as a whole for discharges occurring during the period from October 1, 1997 to September 30, 1998. The majority of cases reported nationally to UDS fall into stroke or orthopedic impairment groups. In contrast to the United States, at the Mount Sinai Hospital, somewhat fewer patients are classified with stroke or orthopedic conditions, whereas a larger proportion are classified with brain injury, spinal cord injury or medically complex conditions. In fact, The Mount Sinai Hospital treats three times as many patients with spinal cord injury and twice as many patients with brain injury as the norm for most rehabilitation centers across the United States.

To understand the data in Fig. 1, it is important to define what patients are classified in the various impairment groups. Patients with stroke have significant physical disabilities such that they cannot safely return home, yet they show promise for functional improvement. "Brain injury" refers both to non-traumatic etiology such as neoplasms or encephalitis and to traumatic injury from accidents and violence. Neurologic conditions include multiple sclerosis, polyneuropathies, Parkinson's disease, and Guillain-Barre syndrome. Spinal cord injury includes both non-traumatic sources of injury such as neoplasms, stenosis, and myelopathies, and traumatic injury from accidents and violence. Orthopedic conditions include hip fracture, hip replacement, and knee replacement. Debility occurs among patients who have become weakened as a result of prolonged hospitalization other than for cardiac and pulmonary conditions. Finally, "amputation" usually refers to a lower limb, generally as a sequela of diabetes or peripheral vascular disease.

TABLE 2
*FIM-FRGs, Version 2.0**

Rehabilitation Impairment Category (RIC)	Number of FRGs in RIC	R^2 LOS
1. Stroke	9	0.26
2. Non-traumatic brain injury	4	0.24
3. Traumatic brain injury	5	0.32
4. Traumatic spinal cord injury	4	0.23
5. Non-traumatic spinal cord injury	4	0.30
6. Guillain-Barre	2	0.30
7. Neurological	2	0.13
8. Lower extremity fracture	4	0.09
9. Joint replacement	7	0.16
10. Other orthopedic	2	0.08
11. Lower limb amputations	2	0.07
12. Other amputation	1	—
13. Osteoarthritis	2	0.12
14. Rheumatoid Arthritis	2	0.10
15. Cardiac	2	0.15
16. Pulmonary	3	0.19
17. Pain	2	0.02
18. Major multiple trauma (MMT)	2	0.18
19. MMT with brain/spine injury	3	0.37
20. Miscellaneous	3	0.15
Evaluation admission only	2	0.08
Overall system	67	0.32

* Adapted from Stineman et al., Health Services Research, 1997, 32, 4, p 537.
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Within each RIC, a number of Function-Related Groups (FRGs), analogous to DRGs, are meant to explain resource consumption. In the latest FIM-FRG model, the motor subtotal score of the FIM assessment (see Table 1) and age are used to develop distinct FRGs using a statistical methodology that classifies homogeneous groupings of patients similar to the methodology used to develop DRGs. In a few FRGs, the cognitive subtotal score of the FIM is used (see Table 1). From the 20 RICs, 67 FRGs were derived. Overall, FRGs explain 32% of the variance in LOS (15), similar to the predictive power of diagnoses in DRGs (16). Stineman and colleagues attempted to put ICD-9-CM codes or major diagnostic categories into the equation to define FRGs, but the increase in explained variance was negligible.

Functional outcomes vary by the types of patients who are treated. Different types of impairments mean that there will be different levels and types of functional gains. This is why an accurate case mix measure is imperative if these measures are to be used for reimbursement. Fig. 2 illustrates outcomes for the major impairment groups at the Mount Sinai Hospital from October 1997 through September 1998. These functional outcomes are approximately the same as for the population of subscribers to UDS across the United States. Most notable about this figure are the differences in functional ability at the time of admission and the differences in functional gain made during the rehabilitation stay, among the impairment groups, pointing to the heterogeneity in functioning among rehabilitation patients. For example, both brain injury and spinal cord injury patients are admitted with low FIM scores. Brain injury patients, however, tend to have both physical and cognitive disabilities. During the rehabilitation process, both cognitive and motor functioning improve. Among spinal cord patients, there is

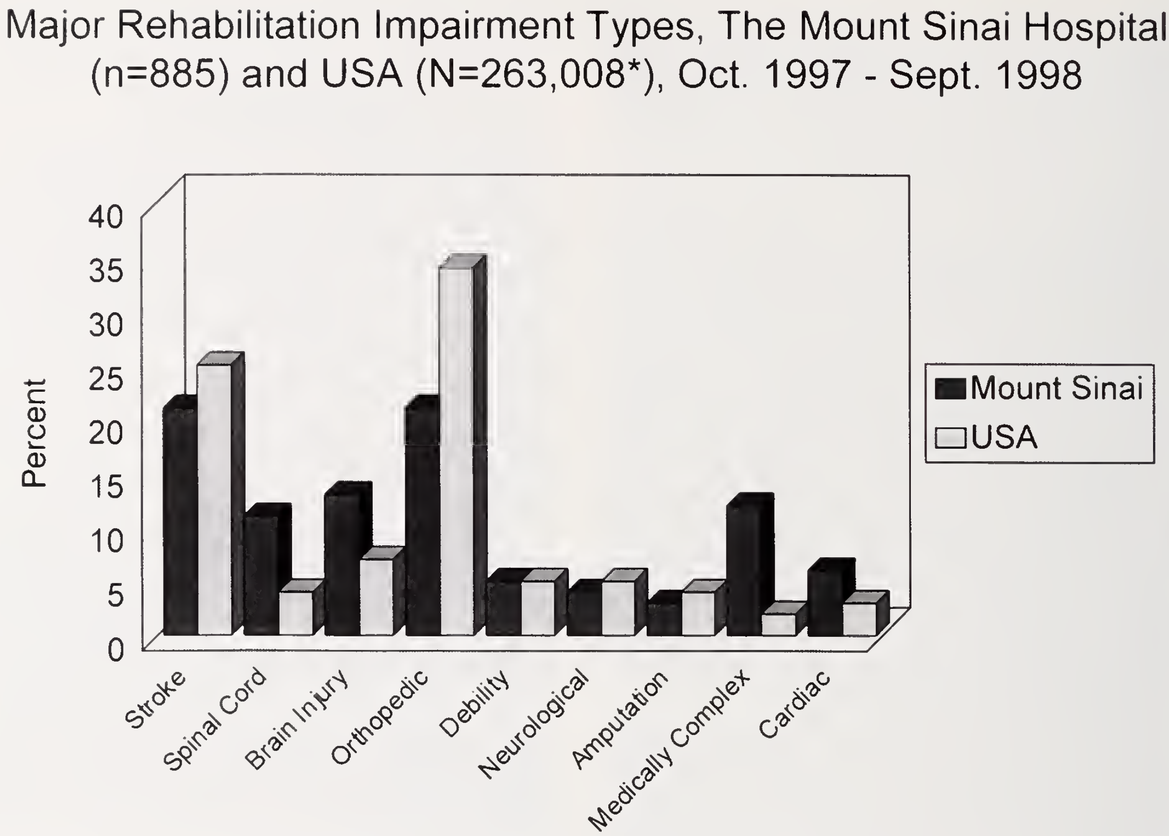

Fig. 1. Major rehabilitation impairment types, The Mount Sinai Hospital (n=885) and USA (N=263,008*), Oct. 1997–Sept. 1998.

* Source: Reprinted with permission of the Uniform Data System for Medical Rehabilitation (UDSmr/SM), State University at Buffalo, 232 Parker Hall, Buffalo, NY 14214.

often no cognitive impairment, but motor impairment is substantial. However, in all groups, statistically significant gains are made between admission and discharge. A detailed discussion of outcomes and LOS for specific FRGs within RICs is available in Stineman, Hamilton et al. (17).

Stineman's work has recently been validated with some modifications by Carter et al. (16), under contract with the Health Care Financing Administration (HCFA), which oversees Medicare payment and policy. Carter's aim was to determine whether the FIM-FRG would be an adequate basis from which to develop a case mix measure which would in turn serve as a basis for a rehabilitation PPS. FIM data were matched by case to Medicare claims files. Carter's validation model used a somewhat different case mix than is observed in the population of persons receiving inpatient rehabilitation, because most persons younger than 65 are not covered by Medicare. For example, traumatic spinal cord injury and traumatic brain injury tend to occur in younger populations, and they were underrepresented in Carter's Medicare population. Carter's model reduced the number of RICs to 18 by putting Guillain-Barre into the neurological RIC, and multiple trauma with brain and spinal cord injuries into the major multiple trauma RIC (see Table 2). Carter and colleagues also reduced the number of FRGs within any RIC to 5 or fewer.

Conceptually and structurally, Carter's model departs from the FIM-FRG model in two important respects. The first change in the model is the inclusion of ICD-9-CM codes for the purpose of recording the presence or absence of comorbidities or complications. This dichotomous variable is analogous to the DRG variable noting the presence or absence of comorbidities and complications. While statistical explanation of LOS was not greatly increased by including comorbidities or complications, the research team thought it clinically important.

The second modification to the model included a variable for interrupted stay. Interrupted stays occur when patients become acutely ill and cannot participate in therapy for a period of time. While only 3–4% of patients

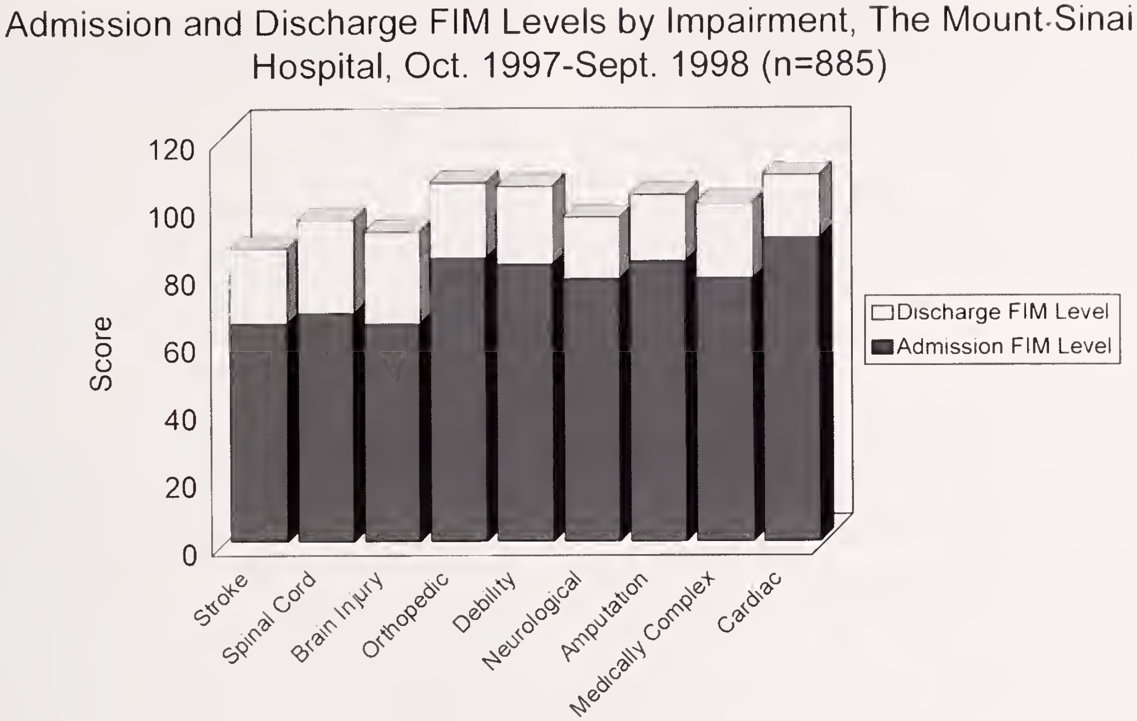

Fig. 2. Admission and discharge FIM levels by impairment, The Mount Sinai Hospital, Oct. 1997–Sept. 1998 (n=885).

FIM range: 18 – 126; Source: Department of Rehabilitation Medicine.

nationally experience interruptions (18), their total LOS is much longer than that of other patients, and Carter and colleagues found that interrupted stay costs were 40 – 60% higher than those for comparable patients with no interruption.

While one may conclude that the FIM-FRG model is able to explain resource use at an acceptable level, it remains empirically untested as a basis for a payment system. The FIM-FRG is a useful model in acute medical rehabilitation settings, but it may not apply to other post-acute care settings such as nursing homes, where patients receive less than three hours of therapies a day. The FIM-FRG model may not be applicable to nursing homes because there are differences in intensity and resources used in the nursing home compared to the acute medical inpatient rehabilitation setting. In addition, there is considerable functional and medical heterogeneity between nursing home and rehabilitation populations. To determine the extent of heterogeneity of patients and resources, HCFA is examining a number of broader-based classification systems in an effort to determine which would be the most efficient and effective for the purposes of payment.

The most recent Congressional mandate to develop a prospective payment system for settings previously exempt from PPS, such as acute medical rehabilitation, was included as part of the Balanced Budget Act (BBA) of 1997 (PL105-33). In the BBA, HCFA is mandated to implement a PPS for all post-acute care services, including rehabilitation, beginning in 2000 with a three-year phase-in to be completed in 2002 (BBA, 1997). The phase-in date, however, is likely to be later than the year 2000. HCFA is considering the use of an alternative tool now being tested in skilled nursing facilities. This is the Resource Utilization Groups or RUG-III system (12), derived from a larger assessment tool (19). The RUGs system has 44 categories of care, including 12 levels of rehabilitation care. In recent work, Fries and colleagues (19) have shown that RUGs explain more than 50% of the variance in resource use in nursing homes. However, resource use in nursing homes is defined as provision of nursing services only, not services from other health professionals such as rehabilitation therapists.

The benefit of the RUGs system is that groups of patients can be compared across types of facilities (i.e., rehabilitation units, nursing homes, home care), to develop equities in service delivery and payment, to reduce overlaps in service delivery and to achieve cost efficiency. However, the RUGs system is based on reimbursement for services given, which provides an incentive for more services, thereby driving up costs (12). Additionally, there is evidence that the RUGs system does not explain resource utilization well among rehabilitation patients, nor do FIM scores explain resource utilization among nursing home rehabilitation patients with hip fracture or stroke (20). Issues of classification systems and payment mechanisms will continue under HCFA's Medicare demonstration programs.

Future Directions

Eventually there will be a PPS for inpatient rehabilitation services under Medicare, which considers rehabilitation as a post-acute care setting. Whether payment will be based on the FIM and RUG-III system embedded in the Minimum Data Set or some other measure of resource consumption has not yet been determined by HCFA. Much pressure has been put on HCFA by professional rehabilitation organizations to include the FIM motor items as part of the Minimum Data Set, since the motor portion of the FIM explains length of stay and resource consumption better than the RUG-III system, excluding FIM items in the rehabilitation setting.

As managed care increases its penetration into the health care insurance market, lengths of stay could be driven down by restrictions in rehabilitation benefits, moving patients more rapidly into outpatient or home-based rehabilitation. The risk in this scenario is that some patients may be medically fragile, and readmissions to either acute care or rehabilitation could erase potential savings by managed care companies. Readmissions should be closely monitored by hospital quality assurance committees in the future.

Rehabilitation philosophy and policy are moving beyond the assessment of patients at admission toward an accountability model of rehabilitation services, i.e., outcome-based measurements. Recent academic and clinical research has reflected this concern. For example, Stineman has recently proposed an outcomes-based model using both the discharge and admission FIM (21) or functional gains made during rehabilitation stay (22). CARF also proposes to move increasingly in this direction in its standards for the program evaluation role in medical rehabilitation.

Although the FIM-FRG methodology achieves its intent in development of a reimbursement mechanism and is more equitable in terms of reimbursement, there have been several criticisms of function-based systems to be used in reimbursement schemes. These criticisms may be extended to any measures which are done only on admission. The most important criticism is that there are no incentives to maximize patient functional outcome (23). Assessment of patient functional ability only on admission determines patient classification for presumed resource consumption, but not what services and other resources are actually delivered. Because outcomes are not measured, i.e., the difference between admission and discharge FIM levels, there is incentive for reducing costs by reducing LOS without a commitment to employing more resources for improving outcomes.

Another weakness of a case-based payment system is that patients who are expected to need heavy care may be denied access to rehabilitation facilities. For-profit institutions and facilities not associated with medical schools and therefore without an inherent interest in teaching and learning may be particularly prone to denial of heavy care cases.

Finally, there are "gaming" issues in any type of prospective payment system. Just as there has been "DRG creep," where acute care patients may be coded in such a way as to maximize illness characteristics to receive higher payment under a higher level DRG category, so, too, with any functional status measure, patients may be "coded down" on functional status measures on admission, to maximize reimbursement. The more statistically valid the assessment tool used to measure functional status, the less room there can be for "gaming" the system.

In sum, the organization and delivery of rehabilitation services will be in a state of flux as public policy mandates and statutes are put into place. The rehabilitation community, however, seems to have taken the debate a step further by building accountability into outcomes-based measures to better understand service efficacy.

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Primary Care for People with Disabilities

David C. Thomas, M.D.

Abstract

People with disabilities are a unique population. Although there have been great advances in their care, access to reliable and consistent primary health care remains a difficult issue for many of these patients after discharge from medical rehabilitation units. Many of these health care needs are not unique to this patient population, but become compounded or exacerbated in people with disabilities. The effects of physical impairments on these patients' health need to be recognized. Specific attention must be paid to prevent the occurrence of secondary disabilities, which can drastically affect their independence. Ultimately, proper attention to the health care needs of people with disabilities will result in greater independence and improved health among this population. **Key Words:** Primary care, disability, preventive health, health maintenance.

Introduction

The specialty of Physical Medicine and Rehabilitation (PM&R) focuses on the health care needs and restoration of function, of people with physical and cognitive impairments. Since the beginning of the 20th century, and especially since World War II, an increasing number of persons with severe impairments have been living longer.

Various advances in health care technologies since the 1930s and 1940s have increased the survival rates of persons with disabilities. Important developments have occurred in the area of antibiotics, acute trauma care systems (especially as a result of WWII), respiratory support systems (negative pressure body respiration, then positive pressure systems), and finally, advances in cardiopulmonary resuscitation methods. Rehabilitation programs began to develop during this period, as a response to the increasing number of individuals with severe disabilities who were living longer and more productive lives despite their permanent impairments.

Concomitantly, societal attitudes have changed toward people with disabilities. These changing attitudes ultimately resulted in the passage of the Americans with Disabilities Act, which entitles all persons with disabilities to fair and equal access to environment services and opportunities.

Despite great strides over the past half century, there are still many barriers for the person with a disability. Access to a reliable, ongoing source of primary health care remains one of the major unresolved issues for people with disabilities who are discharged from medical rehabilitation units (1).

Unique Issues for People with Disabilities

Many of the medical conditions encountered by people without disabilities are also relevant to those with disabilities. In addition, the wide variety of impairments present differently in individuals with disabilities because of varying pathophysiologies, co-morbidities, and functional consequences. However, persons with disabilities may be more vulnerable to common health condi-

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tions, and they may present differently or require a more lengthy therapeutic regime that takes into account their underlying impairment and functional limitations.

DeJong (2) points out six ways in which the ongoing health care needs of persons with a disability are different from those of the general population:

- The narrow margin of health, which necessitates careful monitoring in order to avoid medical problems. This is relevant to certain health conditions shared by people without a disability (i.e., upper respiratory tract infections, pneumonia), but especially relates to conditions found in persons with disabilities (e.g., pressure sores). These impairments and functional limitations result in a thinner margin of health, leading to increased medical problems.

- Limited availability of "insurance" or prepaid coverage for health care and preventative medicine.

- The risk of acquiring a chronic health condition at an earlier age than is usual in the general population (e.g., coronary artery disease in the individual whose mobility is limited; or in whom a lack of aerobic exercise leads to increased weight gain and an earlier onset of type II diabetes).

- Onset of a new health condition, which leads to a secondary functional loss, with resulting significant physical limitations and increased dependence.

- A more complicated and prolonged course of treatment before restoration of their previous functional status.

- The need for durable medical equipment devices and other assistive technologies which require detailed knowledge by both the prescriber and patient.

Identifying the Problem

In 1988, The American Congress of Rehabilitation Medicine adopted a white paper on the post-rehabilitation health care needs of people with disabilities. It was updated in 1993 (1). Its main point is that people with disabilities are not well served by the health care system after discharge from medical rehabilitation units. This lack of access to primary care then leads to recurrent but often preventable health problems.

These post-discharge health problems lead in turn to increased rehospitalizations compared to the general population, often approaching 40% in the first year. The two leading causes, urinary tract infections and pressure sores, are preventable (3).

Aging with a disability presents its own unique difficulties. The health care needs increase markedly in this population. They are living long enough to experience the chronic health problems faced by the able bodied (e.g., osteoporosis and cardiovascular disease). But these conditions tend to surface earlier and lead to worse consequences for persons with physical disabilities. These new chronic conditions tend to aggravate existing functional losses and then compromise a person's ability to work and live independently.

The provision of long-term services in the form of personal assistance remains a very important issue for a person who requires assistance with personal care. Nosek (4) showed that inadequate personal assistance led to extended hospital stay and inability to maintain good physical and mental health.

As disproportionately high users of health care services, people with disabilities have been grossly affected by the current trends in health care reform. Health insurance continues to become less accessible, less affordable, and less adequate in its coverage for a population of people who require it most.

Finally, access to primary care is an important issue for persons with disabilities particularly since physical barriers may be present. More time and effort may be required to attend to the problems presented by those with disabilities. Moreover, the staff may not know how to safely handle the mobility-impaired patient.

Health Promotion Needs of Persons with Disabilities

A permanent disabling disorder or a chronic illness leads to additional specific needs. These include prevention of secondary disabilities and management of the unique issues of aging with a disability. In addition, these patients need standard health maintenance and wellness promotion. Even though there is no consensus among The American College of Physicians (ACP), The Canadian Task Force (CTF), and the U.S. Preventive Services Task Force (USTF), most recommendations of the expert panels call for selective screening, counseling, and prophylaxis (5).

Wellness Promotion and Health Maintenance

It is important to monitor those factors which could lead to decreased independence in persons with disabilities. Nutritional counseling, to help them maintain a desirable weight and limit fat and cholesterol intake, is important. Height on initial visit and weight at least every year should be obtained in order to calculate the patient's body mass index (BMI, kg/m^2). Good dental health should be encouraged. Screening for glaucoma and periodic refraction is necessary, to limit worsening of functional status secondary to deteriorating vision. Maintaining good cardiovascular fitness is paramount in the mobility-impaired patient. Blood pressure should be checked at every visit and a periodic ECG should be obtained for all patients over the age of 40 with risk factors for coronary artery disease, or those who plan on starting an exercise program after a prolonged period of immobility. Exercise stress testing is not recommended routinely, but should be considered for the patient over age 40 who has risk factors for coronary artery disease. Obviously, the patient's level of mobility will dictate the type of stress test (i.e., treadmill vs. chemical). Exercise consistent with the patient's condition should be encouraged. A cognitive and functional assessment of all elderly patients should be performed; it should include screening for depression.

The selective use of laboratory screening tests is also recommended, bearing in mind that recommendations put forth by the three expert panels may differ (5). Each patient encounter should be individualized. A hematocrit is not routine, but should be obtained for low socioeconomic and institutionalized elderly patients. Obtain a urine analysis for patients over 60 years old and all diabetic patients. Fasting plasma glucose is not routinely recommended except in those with a family history of diabetes, a history of gestational diabetes or obesity. A serum cholesterol should be obtained at least by age 30 and then every five years. The ACP and USTF recommend thyroid function testing in women with nonspecific symptoms after the age of 50 and 60, respectively. HIV serologic screening is necessary in all patients with high risk behavior or who received blood transfusions between the years 1978 and 1985. Syphilis serologic screening should be done for all patients with high risk sexual behavior. Routine prostate specific antigen is not recommended by any of the three expert panels. Further use of blood tests is decided based on the history and physical.

Tuberculin skin testing is needed for all patients exposed to tuberculosis, those with HIV and those taking high dose steroids. A screening chest x-ray for lung cancer is not recommended by any panel. Bone density analysis should be considered in perimenopausal women, those with early menopause and slender women. A yearly routine mammogram is recommended for all women from age 50, and in those after the age of 35 with a premenopausal first-degree relative who had breast cancer. Routine cervical cytologic screening is routine for all women after the age of 20 or at the onset of sexual activity.

Stool for occult blood should be obtained after the age of 50 from all patients, and after 40 from those with a first-degree relative with colon cancer or history of inflammatory bowel disease. Routine sigmoidoscopy is recommended by the ACP after the age of 50 or after the age of 40 for those with a first-degree relative with colon cancer, a history of inflammatory bowel disease, or endometrial, breast, or ovarian cancer. If there is a first-degree relative with colon cancer, a history of ulcerative colitis for more than 10 years, adenomatous polyps, or familial polyposis, a colonoscopy should be obtained.

Vaccinations and Chemoprophylaxis in Adults

An updated vaccination record should be maintained in each patient's chart. The role that a patient's disability plays in altering the time at which the patient should receive a vaccination has not been fully researched. The recommendations were reviewed by *The New England Journal of Medicine* (6) and the *Annals of Internal Medicine* in 1996 (7).

The pneumococcal vaccine is recommended in all patients after age 65, and in those older than 18 with chronic organ disease, HIV disease, sickle cell disease, and asplenia, those older than 55 who are institutionalized, and those with spinal cord injury (7, 8). This vaccine should be considered in any patient with a neuromuscular disease. The influenza vaccine is recommended yearly for those older than 65 and for any adult with chronic disease, living in a chronic care facility or who is employed (6). All adults should receive a tetanus-diphtheria vaccine every 10 years (6). A hepatitis B vaccine should be given to health care workers, intravenous drug users, and patients with multiple sexual partners (6). The hepatitis A vaccine should be offered to all persons traveling to an endemic country, in addition to homosexual men, intravenous drug users, those with chronic liver disease, and those with an occupational risk (7).

A Rubella level should be checked in women of childbearing age and offered to all adults. The measles vaccine is given to all patients born after 1956, and a revaccination is necessary for those who received the vaccine between 1963 and 1967. A reliable history of varicella is adequate proof of immunity, but the vaccine should be offered to health care workers, household contacts of immunocompromised people, and those with high exposure (school personnel, day care workers, young adults in college or the military). It should not be given to pregnant women.

Lifestyle Issues

Many of these issues are not unique to those with disabilities. However, they are often overlooked in this patient population. It is important to counsel patients on the hazards of substance abuse, and the need to stop smoking and limit excess alcohol. The need for safe sex practices should be emphasized, and birth control should be discussed. Injury prevention, both vehicular and occupational, needs to be addressed. This is especially important for physically impaired persons, working with equipment that has not been adapted to them. The need for stress management and a good evaluation for depression is necessary in these patients, and especially in those over the age of 65. At each visit, an emphasis on monitoring for domestic violence and abuse is imperative in this population.

Secondary Disability Prevention

For those persons living with a disability or chronic condition, it is paramount to their continued independence to prevent the occurrence of a secondary disability. For this could well lead to a loss of work and, more important, to a loss of independence in activities of daily living. The primary health care provider may not be aware of these issues or may not realize the consequences.

It is important to preserve the strength of the patient. The slightest decrease may result in the loss of ambulation or self-care. Simultaneously, the prevention of contractures and skeletal deformities is necessary. The maintenance of good skin integrity and the prevention of pressure sores is paramount in this population. It is also imperative to maintain adequate function of both the bowel and bladder. This should be individualized according to the patient's impairment and disability. The prevention of infection, especially of the bladder and lungs, is a necessity. If these organs are maintained, then the person will be able to preserve his or her functional level of independence. And this ultimately will prevent rehospitalization. Finally, the emotional and social adaptations to living with a disability must be recognized and provided for. Support and training are needed, not only for the patients, but also for the family and the caregivers.

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Repetitive Strain Injury (Cumulative Trauma Disorder):

Causes and Treatment

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Abstract

Backgroud: The computerization of the workforce in the last two decades has led to increases in the incidence of repetitive strain injury (RSI). U.S. Workers' Compensation claims made by persons disabled in the upper extremities in 1989 were estimated to be $563 million.

Method: Through an investigation of factors that increase the likelihood of contracting an RSI in various industries, the authors suggest a relation between workplace conditions, lack of education about causes of RSI and improper use of equipment among contemporary workers.

Results: A medical term which analyzes the unique history and mechanism of the injury and offers a unique regimen of exercise, education, modalities and some pain management has proven to be the most effective treatment for RSI. Damage to muscle and tendon due to RSI generally cannot be surgically repaired. However, specific nerve-related disorders can be treated with surgery if other more conservative treatments prove ineffective.

Conclusion: Through foresight and education, industries in which specific factors render workers more likely to contract RSI can begin to take steps to minimize worker susceptibility to the disorder. Those industries will face large losses due to Workers' Compensation claims, disability pay, lawsuits and ultimately lower productivity. **Key Words:** Repetitive strain injury, cumulative trauma disorder.

Repetitive strain injuries (RSI) are defined as cumulative trauma disorders (CTD) resulting from prolonged repetitive, forceful or awkward movements. These movements result in damage to the muscles, tendons and nerves. RSIs are referred to as repetitive stress injuries, CTDs, repetitive motion disorders, occupational overuse injuries and work-related musculoskeletal disorders. RSIs also can refer to well-defined disorders such as carpal tunnel syndrome (CTS) and tendinitis; or to clinically less well-defined conditions such as tension neck syndrome.

An increasing number of RSIs has occurred during the past two decades. These inquiries now account for more than 50% of all workers' compensation claims, at a cost of about $20 billion a year. The Bureau of Labor Statistics estimates that more than 332,000 cases of disorders were caused by repeated trauma in 1994 (1). From 1984–1994, the incidence rate of these disorders increased from 5.1 to 39 cases per 10,000 full-time workers. These increases may be related to the rapid computerization of the American work force and the rapid increase in industries in which data entry jobs predominate. In 1984, fewer than 25% of workers used computers on their jobs; however, by 1994, more than 47% of workers used computers.

In the workplace, upper extremity RSIs outnumber lower extremity injuries. In 1989, the total U.S. Workers' Compensation costs for upper-extremity CTDs was estimated to be $563 million (2).

The prevalence of neck symptoms, including pain, stiffness and discomfort, affects 10–20% of the adult population annually (3–7). Tension neck syndrome is defined as pain, fatigue and stiffness in the neck muscles. The prevalence of tension neck syndrome ranges from 5% in slaughterhouse workers to 80% of office workers and 100% of film-rolling workers (8). Several studies

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have shown that workers in forceful, repetitive, hand-intensive jobs requiring static neck muscle contraction have a higher prevalence of neck RSIs than workers with less forceful, repetitive jobs (9–12). Other studies revealed that there was an association with an increase in the percent of time typing at video display terminal (VDT) keyboards and the prevalence of neck symptoms (13–14).

Spine-related problems occur with greater frequencies in professions that require lifting and repetitive activity. The prevalence of cervical spondylosis ranges from 14% in dentists, carriers and miners to 84% in meat carriers (8). The annual incidence of cervical syndrome (cervical disk disease) is 5.5 per 100,000 (15). An increased risk of cervical herniated disks is seen with frequent lifting and operating vibrating equipment (16). A significantly increased odds ratio is also seen in slaughterhouse workers, scissor makers and civil servants (8).

Allander (3) reported prevalences of painful shoulder ranging from less than 10% to more than 20%, depending on the age group. Workers exposed to inclement temperatures, such as meat carriers, are consistently more likely to develop shoulder tendinitis. Risk factors most strongly associated with shoulder tendinitis include working at or above shoulder height, heavy lifting and carrying loads supported by the shoulder, maintaining static postures and using implements that cause hand-arm vibration (8). A strong association with shoulder tendinitis is also seen with repetitive movements. Odds ratio ranged from 2.2–10 for studies of heavy lifting and repeated loading of the shoulders in letter carriers (11) and construction workers (17). There was a 1% prevalence seen in sign language interpreters (18) and 31% in sewing machine operators (7).

The prevalence of thoracic outlet syndrome, due to repetitive elevation of upper extremities overhead and/or forward posturing of shoulders, ranges from 1% in slaughterhouse workers to 32% in cash register operators and 44% in assembly line workers (8).

The prevalence of rotator cuff tendinitis ranges from 1% in data entry operators to 69% of industrial workers who work at shoulder level (8).

There are relatively few studies which have looked at the prevalence of epicondylitis in the work place. Current medical research relates this condition to occupations which require overexertion of the finger and wrist extensors while the elbow is in extension. Workers considered at high risk includes garment workers (19), construction workers (20), meat processors (21) and grocery checkers (22).

A review of European literature by Spaans (23) revealed an association between ulnar neuropathy and occupational activities of brass workers, crystal grinders, diamond cutters, enamelers, glass cutters, gold beaters, rollers, telephonists, locksmiths, mechanics, plumbers, stonecutters, and joiners (23). An association was seen in chess players (24), telephonists (25) and clerical occupations (26).

There is consistent evidence from many studies which reveals an association of repetitive hand motions, forceful manual exertions and hand-arm vibration with CTS and hand-wrist tendinitis (27–32). The prevalence of CTS ranged from 0.6% to 61% depending on the occupational group studied (17, 19, 33–36). Studies have revealed odds ratios for CTS and certain jobs range from 1–34 (grocery checkers, such as supermarket checkout cashiers) (37–39). Evidence also suggests that the presence of two or more risk factors can have a highly synergistic effect; e.g., workers who perform repetitive and forceful activities have higher rates of hand-wrist disorders than those who perform either repetitive or forceful activities alone (34–36).

The 1989 National Institute for Occupational Safety and Health Review revealed that only 9 out of 52 cross-sectional studies reported a prevalence rate lower than 20% among workers exposed to hand-arm vibration (40). Odds ratio of greater than 5 was frequently reported for workers exposed to inclement conditions as well as hand-arm vibration (41). Incidence in lumberjacks was 30.6% (42). There is substantial evidence linking the intensity and duration of exposure to vibrating tools, and the risk of developing hand-arm vibration syndrome (43–46).

A common misconception is that RSI is synonymous with CTS. However, in the computer workforce, CTS is found less frequently than deQuervain's tenosynovitis. According to the National Institute of Occupational Safety and Health's study of RSI at US West Communications, 15% of all employees had tendon-related disorders, but only 1% had CTS.

Therapeutic Management

In the treatment of patients with RSI, a team approach is used at Mount Sinai. The team consists of the doctor, occupational and physical therapists, ergonomist and the RSI support group. The goals of management of patients with RSI are: (1) patient education, (2) reduction of pain, (3) home exercise program, and (4) lifestyle changes. Patients are educated about their specific condition and the mechanism that contributes to the injury. Reduction of pain is achieved by several techniques, including modalities such as ice packs and self-monitoring of posture and body alignment. These will be discussed later in this article. The patient is taught how to avoid positions which may exacerbate pain, and to correct body mechanics for performing activities. All patients are instructed in a home exercise program individually tailored to their diagnosis. Home exercise program increases the patients' awareness of their body and enables them to avoid continued injury. It is effective in reducing pain and treatment time in the therapy. An aerobic exercise program is also tailored to their specific medical conditions. In addition, the patient is educated about ways to improve lifestyle so as to prevent further injury. Adequate rest and recovery are necessary to prevent further inflammation.

Another goal is to learn how to perform work activities while supporting a healing process and preventing a recurrence of the injury. This is done with patient education, task analysis, trials of positioning strategies, equipment trials, work behavior and technique retraining, simulation of work activities, and generation of complete specifications and resources. Various equipment is tried, such as split keyboards (fixed and flexible) and track balls of different shapes and sizes. Computer access can be achieved with alternative input devices such as voice recognition and the use of other body parts.

Furthermore, the patient's expectations and goals are established. Dialogue between worker and employer is encouraged in order to set realistic goals. The patient agrees to comply with a plan that is satisfactory and realistic, and a reasonable recommendation is given to the employer.

A comprehensive evaluation is done to document the patient's condition and to plan the appropriate treatment. This evaluation includes past and present medical illnesses; physical activity levels; daily routines and hobbies; a thorough work history with special attention as to when symptoms appeared, and a history of any trauma. Level of pain is documented with pain scales and diagrams. This evaluation enables the patient to discuss his or her pain in an objective manner and allow comparison before, during and after treatment.

A physical exam, which includes range of motion of joints, soft tissue palpation, manual muscle testing, sensory screens, and evaluations of sitting and standing postures are performed. Specific tests for presenting conditions are used to verify diagnosis or objectively document patients' symptoms. For example, to test for tendinitis, the tendons are tested in both lengthened and shortened positions, such as by reaching for the floor and/or ceiling.

A work station assessment is an essential component of treatment of the individual with RSI. An assessment of how the individual performs in the work environment can reveal factors contributing to the injury. Patients are asked to bring photographs or videotapes of themselves while performing duties at their work station, for evaluation. The patient also completes a work sheet of the dimensions of the work space. Positions of pain and of comfort are identified. The majority of patients participating in the Mount Sinai Medical Center assistive technology work station assessment program are office workers who had become injured while using computers. A list of tasks and job description is correlated with short- and long-term vocational goals. This includes identifying the computer tasks, as well as those tasks that support the computer work such as paper management, writing, reading and telephone correspondence.

The acute phase of the RSI is characterized by inflammation and pain with activity, and occasionally, pain at rest. The goal is to decrease edema, reduce pain and educate the patient in proper body mechanics to deter further injury. The patient is educated about his symptoms and the management of his symptoms, the healing process and activity modification. Positioning during sleep is also evaluated and modified, if needed.

Splints may be used to immobilize the involved body part(s) in a position of rest, thus allowing the healing process to occur. If the injury is acute, splints are worn at all times except for periods of exercise and self care. As the pain decreases, the time the splint is worn during pain-free intervals is decreased and functional use of the involved extremity is encouraged. The type of splinting material used varies from thermoplastic to soft, flexible splints. Thermoplastic materials are rigid and used in the acute phase to provide immobilization. Flexible splints are used with patients who are recovering and have a decreasing amount of pain.

Modalities such as heat- and cold-packs are used to decrease pain and edema. Electrical modalities such as transcutaneous electrical nerve stimulation may also decrease pain. Galvanic stimulation and iontophoresis are used to decrease edema and inflammation. Moist heat increases circulation to specific areas and reduces joint stiffness. Ultrasound is used to heat deep muscle groups and large joints.

Additionally, manual techniques are used to reduce edema, decrease myofascial pain, restore normal range of motion and decrease muscle spasm. The patient can be instructed in gentle massage techniques to reduce pain, and range of motion and stretching exercises to assist in improving posture and alignment. Patients are encouraged to take short breaks of about 1 – 10 minutes, 3 – 4 times each work day to perform these exercises.

In the chronic phase of RSI, the emphasis of treatment is on education regarding management of symptoms, exercises to increase cardiovascular fitness, and strengthening exercises for proximal and postural muscles. Work and lifestyle changes are encouraged to promote healing throughout the treatment. Patient education continues with instructions on activity modification to prevent overuse and reinjury. Activities are analyzed and simulated in the clinic to determine which ones exacerbate injury. An aerobic exercise program is recommended to improve cardiovascular fitness. Patients are gradually started on a program of aerobic exercise, beginning with a 10 minute regimen. As fitness improves, they are encouraged to gradually increase to 20 – 30 minutes three times a week, as tolerated.

Medications are used to reduce the pain and inflammation associated with RSI. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for the pain and inflammation caused by RSI. Commonly prescribed NSAIDs include ibuprofen and fenoprofen. More potent and less commonly prescribed NSAIDs are butazolidin, indocin and voltaren. Since side effects can be serious, especially for people over 40. Aspirin and acetaminophen are also used to treat the pain of RSI. Narcotic analgesics are rarely required and should never be continued beyond the first two weeks.

Injections of cortisone are used to treat RSI, but they should be used sparingly, if at all. They are helpful in reducing local pain and inflammation, but can cause tendons to rupture. Cortisone also can be applied in other ways, such as in creams and sprays. It also can be applied via phonophoresis (ultrasound) or iontophoresis (low voltage and low amperage), which allows the cortisone to penetrate through the skin into the soft tissue to reduce inflammation. Trigger point injections with anesthetic have been advocated by some physicians, yet clinical trials demonstrating their efficacy are lacking.

In most cases of RSI, the damage to the muscle and tendon cannot be surgically repaired. However, there are surgical procedures for certain RSI diagnoses (e.g., CTS, Dupuytren's contracture, deQuervain's disease and ulnar nerve entrapment). Surgery is sometimes necessary to preserve nerve function, and when conservative treatments fail.

In an effort to promote their ability to cope with their temporary or potentially life-changing injuries, the patients are referred to the Mount Sinai Medical Center RSI support group, which includes social workers. In addition, they are referred to clinical psychologists.

Conclusion

RSI affects a large percentage of the workforce. People develop RSI because they do not know how to or are unable to protect their muscles, tendons and nerves. The workstation may not be set up properly; they may have never been trained to use their hands properly, or they may be unable to pace themselves. To reverse the damage of RSI, the patients and their work environment need to change; the process begins in rehabilitation therapy. Patients are taught how to pace themselves in order to allow their muscles, tendons and nerves to rest. Pain-induced immobility is replaced by gentle stretching and strengthening exercises. Deep tissue massage breaks down scar tissue built up with overuse. Retraining stops the cycle of reinjury. Therapists can use several techniques to assist in recovery, which include workstation assessment and modification, posture and positioning modifications, exercise programs, patient education, splinting and modalities. Medical management includes pain and anti-inflammatory medications.

With planning and foresight, RSI can be prevented. People who can control their environment and the pace of their work can protect themselves. When there is no control of the pace of one's work, environment or workstation, negotiations with one's employer about safe working conditions must occur. By redesigning jobs, educating the work force about RSI, investing in ergonomic equipment and training employees how to use it can prevent RSI from occurring. However, if factors which contribute to RSI are ignored, industries will face large losses due to Workers' Compensation claims, disability pay, lawsuits and ultimately, lower productivity.

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Osteoporosis and Exercise:

A Review

Parag Sheth, M.D.

Abstract

Background: Osteoporosis is a widespread bone disorder which primarily effects postmenopausal women, with annual costs of six billion dollars. Several studies have looked at the potential value of exercise as an inexpensive and widely available treatment.

Methods: Using Medline, English-language articles published after 1989 in major medical journals and containing the key words "exercise" and "osteoporosis" were obtained. Selected prospective studies which included twenty or more subjects were reviewed with special attention to the exercise portion of the protocol. Studies felt to be historically important were also reviewed.

Results: Quality of studies, design types and exercise intervention varied greatly. Detailed exercise protocols, high compliance rates and low drop-out rates appeared to favorably effect results.

Conclusion: As a whole, the literature suggests that exercise induced improvement in bone mineral density in select individuals. Based on the review the author suggests an ideal program.

Key Words: Exercise, osteoporosis, bone mineral density, review.

Osteoporosis is characterized by abnormally low bone mass and micro-architectural deterioration of bone tissue, leading to an increase in bone fragility and a consequent increase in fracture risk (1). The costs of the complications of osteoporosis are estimated at six billion dollars in 1992 (2). Moreover, as the population life expectancy increases, the problem of osteoporosis is likely to grow.

The major complication of osteoporosis is fracture. Fractures are most common in the femur and spine, and their incidence increases exponentially in the later years of life (3). Each standard deviation decrease in femoral neck bone mineral density (BMD) increases the age-adjusted risk of hip fracture 2.6 times (5). BMD accounts for 80 – 90% of the variance in the strength of the proximal femur (5). BMD assessment can be performed by various methods. Conventional radiographs are considered unreliable. The first quantitative methods developed were single photondensitometry and photon absorptiometry. They measure primarily cortical bone of the appendicular skeleton. More recent techniques can quantify bone mineral content in the spine, the site of early osteoporosis. Dual photon absorptiometry (DPA) and dual x-ray absorptiometry (DXA) measure an integral of compact and cancellous bone of the axial or entire skeleton. Quantitative computed tomography (QCT) measures pure trabecular bone. Most recent investigations favor DXA because of the shortened exam time and greater accuracy compared to DPA, and lower radiation exposure compared to QCT (6).

Bone mineral density may be a modifiable risk factor for fracture, through exercise. This was suggested by early longitudinal studies among cross country runners (7, 8). The first major study to investigate the role of exercise was reported by Lane et al. (9). They compared the BMD of forty-one members of the "50 Plus Runners Association" with age-matched controls

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and found that the runners had about 40% greater BMD. In 1989, Michel et al. (10) expanded this study group to include more females and focus on the amount and types of exercise performed (running, dancing and brisk walking). A strong correlation was found between BMD and up to 300 minutes of exercise per week, but the five women who exercised more than 300 minutes experienced no additional benefit.

In 1989, a similar study by Kirk et al. (11) used a smaller sample size but closely matched controls (T4, FSH, VO_2max, Vitamin D levels). The researchers found no improvement in vertebral BMD in postmenopausal subjects, only in the premenopausal group (not previously reported). There are significant methodological differences between these studies, making comparison difficult. But they were historically important and served as a springboard to a large number of more recent investigations. For example, a 1996 longitudinal study by Orwoll et al. (12) of more than seven thousand ambulatory women found that general activity level and muscle strength (and, importantly, increased body weight) were associated with increased BMD. Since then, there have been prospective randomized trials which have tested the potential value of exercise in improving BMD.

The goal of this article is to provide the reader with a critical review of important recent exercise intervention trials. Earlier studies have been reviewed elsewhere (13). The physiatrist frequently deals with detailed exercise prescriptions and issues of patient compliance. Some studies involve comparison of multiple intervention (e.g., estrogen, calcium). Special attention will be paid to the exercise portion of the methodology and the stated or likely patient compliance, in order to assist the reader in making realistic conclusions about the types and intensity of exercise required. Specific recommendations and a review of the present understanding of how exercise may affect BMD will follow.

Dalsky et al. (14) reported the first prospective study of the effect of exercise on BMD. Her group used DPA to compare lumbar spine mineral content in 17 exercise volunteers and 18 sedentary controls whose average age was 62. Exercise consisted of three sessions per week of walking, jogging and, eventually, stair climbing, for a total of 50–60 minutes at 70–90% of maximal oxygen capacity. Additionally, each participant performed 15–20 minutes of rowing or cycling. BMD was measured at nine months, and for some subjects at twenty-two months. BMD increased 5.2% at nine months and 6.1% at twenty-two months, compared to an expected decline of 1.4% in controls. Those who stopped exercising at nine months had their BMD decline to only 1.1% below their baseline after twenty-two months. Although these gains in BMD are among the most substantial reported to date, these subjects were admittedly not randomized in this study, but rather had volunteered to exercise. Indeed, two subjects initially in the exercise group were converted to controls when their initial exercise attendance was poor.

In 1991, Notelovitz et al. (15) published a prospective randomized study of the effects of variable resistance (Nautilus®) exercise on BMD, again using DPA. Twenty subjects who had undergone surgical menopause and were using hormonal replacement therapy (HRT) were randomized into two groups: exercise and sedentary controls. The exercise group worked on a one-to-one basis with an "exercise trainer" three times per week for 15–20 minutes for one year. They participated in at least 70% of their sessions. BMD gains were substantial for the radial mid-shaft (4%), spine (8%) and total body (2%). Of note, subjects were younger in this study (average age 43) than most postmenopausal subjects, because they had undergone surgical menopause. Also the exact onset and duration of HRT are not given, which may discredit the results.

The first large prospective study on this topic was by Prince et al. (16). This two-year study compared sedentary controls, exercise subjects, exercise plus calcium, and exercise plus HRT. The mean age of the subjects was 56. Forty postmenopausal subjects were in each group, all with BMD one standard deviation below the fracture threshold at the distal radius, as determined by CT scanning. The rate of bone loss was similar for the exercise group and the sedentary controls. Calcium slowed bone loss, while the HRT group gained bone mass. This important study concluded that HRT should be used in the treatment of osteoporosis. As a study of the role of exercise, however, it should be viewed with caution, since exercise consisted of only one hour of supervised low impact aerobics per week. Compliance was less than 50%. Moreover, the wrist site was poorly chosen as an area likely to be effected by a traditional low impact exercise program.

In 1994, Nelson et al. (17) were the first to use dual x-ray absorptiometry to perform a randomized, prospective control trial of the effects of high intensity strength training. The average age of her subjects was 61. Under close supervision by a physical trainer (two subjects per trainer), 45 minutes of exercise were performed on pneumatic resistance machines twice a week for one year at 80% of one repetition maximum (1RM) (80% of the maximal weight that could be lifted once on a given machine). The values for 1RMs were reestablished every four weeks. Exercise was directed at the major proximal muscle groups and an exact protocol is described (three sets of 8 repetitions, with each repetition lasting 6–9 seconds and two minutes between sets). Attendance was 87%. Significant gains in BMD were noted at the femoral neck and lumbar spine. Muscle mass, strength and balance also significantly improved.

In 1995, Pruitt et al. (18) compared high and low intensity resistance training (80% vs. 40% of 1RM with the same total work) in a group of older postmenopausal subjects whose average age was 68. The protocol described was quite similar to Nelson's discussed above and is well outlined by the authors. However, no significant changes in BMD were found. As the number of subjects per trainer is not detailed, it appears that they were trained as a group. Many subjects dropped out of this study. Strength gains, although statistically significant, seem surprisingly small after one year of training (10–66%). For example, the increase in lateral pull- down strength found in Nelson's group was 76% while the change was only 41% in this study. The authors also note that their subjects' baseline BMD was unusually high and felt that this may have prevented further gains. It may also be that the older age of the subjects or the lower level of supervision made the exercise routine less rigorous.

The next two important recent contributions to the osteoporosis and exercise literature involve studies of weight-bearing exercises such as walking, jogging, or aerobics, as opposed to the resistance-training protocols cited above.

In 1995, Kohrt et al. (19) published a one-year interventional trial comparing the combined and separate effects of HRT and weight-bearing exercises in 32 subjects with an average age of 66. Exercise consisted of 2 months of low intensity exercises followed by 9 months of more vigorous exercise (jogging or stair climbing) for 45 minutes between three and five times per week at 65–85% of maximal heart rate (confirmed weekly by heart rate monitoring). The program was individualized, with new goals set weekly. In the last 4 weeks of the study, participants were still averaging 3.3 sessions per week. Exercise or HRT alone caused a significant improvement in BMD of the lumbar spine, hip and femur. HRT plus exercise had an additive effect at the lumbar spine and synergistic effect on total BMD. Because of the small sample size, subjects were not randomized, but assigned to treatment groups on a matching basis for body weight.

Prince et al. (20) published another article on osteoporosis and exercise in 1995. They compared the effects of calcium and exercise on BMD during a two-year interventional trial. BMD was measured via DXA in the lumbar spine, at three sites at the hip and two tibial sites near the ankle. The average age of subjects was 63. One gram of calcium supplement in either tablet or powdered milk form was found to be beneficial in preventing bone loss at the intertrochanteric hip site and ultradistal tibia. The calcium and exercise group had less bone loss only at the femoral neck site when compared to calcium alone in either form. Again, the actual amount of exercise performed by subjects in this study needs to be carefully scrutinized. Subjects were "asked to perform" three additional hours of weight-bearing exercise per week (two of which could be self-reported walking). No information is given as to the level of supervision or modification of goals during the two-year period. Compliance was only 39%.

As is generally the case with a relatively new area of research, larger, more detailed studies would be of benefit in reaching more definite conclusions. It is worth observing, however, that all of the published work that showed a strong benefit from exercise reported at least two of the following elements: a highly detailed exercise regimen (including type, frequency, intensity and duration), frequent revision and advancement of the exercise goals, close supervision of the subjects, low drop-out rates, high compliance rates, and highly motivated subjects. Significant improvements have been noted with both resistance-type training, and aerobic training, although resistance protocols generally appear to be more effective. A few studies have followed patients for more than one or two years to assess long-term benefits and compliance. These studies have shown a trend toward reversion to pre-exercise levels with discontinuation of exercise (14, 21).

Optimal mechanical strain to enhance bone remodeling has only been tested in animal models. A series of studies by Lanyon and Rubin in isolated turkey or rooster ulna osteotomy preparations have been the most comprehensive (22–24). Changes in bone mass were more responsive to strain magnitude than load cycles. It may be, therefore, that the development of muscular fatigue is an important precondition or stimulus to bone remodeling.

Based on this review, the author feels that the ideal exercise to stimulate BMD would involve progressive resistive training using several slow repetitions at 70–80% of the one repetition maximum until the muscles feel fatigued. The exercise should be performed at least three times per week for 30 minutes and continued for one year. The 1RM should be adjusted monthly and all of the proximal large muscle groups should be exercised. Walking alone is probably not enough stimulus for BMD changes. The reader is cautioned that this program may be too strenuous and potentially dangerous for elderly patients with concomitant medical problems. Also, patients with a history of vertebral compression fracture should avoid lumbar flexion exercises because of the suspected risk of further fractures (25).

The author believes that, for the well-chosen and motivated individual, exercise is of benefit in improving bone mineral density. It is equally important to remember that there are other clearly well-documented benefits to any exercise program in all postmenopausal subjects, regardless of the potential for BMD change. Exercise has recently been documented to prevent falls and fractures (26). Aerobic exercise performed regularly will diminish the risk of heart disease (27). Finally and most important, patients with osteoporosis who exercise regularly have an improved quality of life (28, 29).

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Treatment with an Anabolic Agent Is Associated with Improvement in Respiratory Function in Persons with Tetraplegia: A Pilot Study

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Abstract

Background: Pulmonary complications are a major cause of morbidity and mortality among individuals with cervical spinal cord lesions. Strengthening of the respiratory musculature may reduce these complications. Anabolic steroids have been used to increase muscle mass and improve muscle performance. Oxandrolone, an anabolic steroid, may have beneficial effects on breathing in persons with tetraplegia.

Methods: The effect of one-month treatment with oxandrolone on weight gain and pulmonary function was studied in ten subjects with complete motor tetraplegia. Spirometry, maximal inspiratory and expiratory pressures, and resting self-rating of dyspnea (Borg Scale) were measured at baseline and repeated again at the end of one month of oxandrolone therapy (20 mg/day). Serum lipid profiles and liver function tests were performed before and after treatment. A paired t-test was used to determine pre- and post-treatment differences on the dependent variables. Percent change from baseline was calculated for each variable and tested using a one-sample t-test.

Results: On average, the subjects gained 1.4±1.5 kg, a 2±2% increase in weight ($p=0.01$). A significant, 9±2% improvement was found in the combined measures of spirometry ($p<0.005$). Maximal inspiratory pressure improved an average of 10±7% ($p<0.001$). Maximal expiratory pressure improved 9±13% (non-significant). Subjective self-rating of dyspnea decreased an average of 37±28% ($p<0.01$).

Conclusions: In healthy subjects with tetraplegia, the use of oxandrolone was associated with significant improvements in weight and pulmonary function, and a subjective reduction in breathlessness. Therefore, oxandrolone may be indicated to strengthen respiratory musculature in individuals who have tetraplegia and ventilatory insufficiency aggravated by superimposition of pneumonia or other such conditions. However, long-term use of oxandrolone may not be indicated, due to the adverse complications associated with this class of agents. **Key Words:** Anabolic agent, oxandrolone, breathing, pulmonary function, tetraplegia, spinal cord injury.

Background

There are approximately 200,000 individuals with spinal cord injury (SCI) in the United States today, with 7 – 10,000 new cases of traumatic SCI occurring each year (1). Slightly more than half of these injuries occur at the cervical level of the spine (2). Cervical paralysis and immobilization can have catastrophic impact on the respiratory muscles, which receive segmental innervation from C_1 through T_{12}. Complete transection of the spinal cord above C_3 causes paralysis of all muscles of respiration, thereby necessitating breathing support from mechanical ventilation. Injury below C_3 partially spares inspiratory muscles, including diaphragm, scalenes, and sternomastoids, but disrupts all muscles of expiration, which are innervated by nerves originating in the thoracic and lumbar spine. As a result of respiratory muscle weakness, ineffective cough and retention of airway secretions frequently lead to atelectasis and pneumonia, the two most frequent causes of morbidity and mortality in the acute period of injury (3 – 5), as well as in those surviving more than 6 months (6). This respiratory muscle weakness has been well documented to cause mild to severe restriction and a restrictive-

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like pattern of spirometry in individuals with tetraplegia (7–11). Individuals with tetraplegia have been found to report a high prevalence of breathlessness (12).

Anabolic steroids have been used to increase muscle mass and thereby improve performance and function. Clinical trials have demonstrated that oxandrolone, an anabolic steroid, is a safe and effective oral adjunct to promote weight gain, predominantly lean tissue, in a variety of pathophysiological conditions, and that it has low potential for androgenic effects (13, 14). Unlike many other anabolic steroids, oxandrolone undergoes little overall metabolic transformation in the liver, and it is well tolerated in men and women (13). Oxandrolone offers potent anabolic activity, which is estimated as 6.3 times greater than that of methyltestosterone (14). Because oxandrolone may have an anabolic effect on the muscles of respiration, our group investigated the potential of this agent to improve measures of breathing in individuals with tetraplegia.

Methods

Subjects

Subjects were recruited for the study based on the inclusion and exclusion criteria. The inclusion criteria consisted of: (1) cervical spinal cord injury more than one year and (2) ability to follow instructions to participate in the study. The exclusion criteria consisted of: (1) pre-injury history of pulmonary disease or respiratory symptoms; (2) active pulmonary infection; (3) receiving medications known to alter airway tone; (4) current smokers who smoke more than $^1/_2$ pack/day; (5) diabetes mellitus; (6) abnormal liver function tests (LFTs); and (7) serum albumin <3.5 g/dL. Ten male subjects with complete motor tetraplegia were enrolled in this study. Four subjects had complete sensory and 6 had incomplete sensory SCI. Three subjects had lesions beginning at C4; seven subjects had lesions beginning at C5. One subject was a current smoker of less than $^1/_2$ pack/day; the other 9 subjects were nonsmokers. All subjects were currently healthy with no pulmonary complications. However, the restrictive-like pulmonary defect commonly seen in those with cervical spinal cord lesion (6–11) was demonstrated in our subjects. Institutional Review Board approval was obtained from the Veterans Affairs Medical Center, Bronx, NY, and informed consent was given by all subjects prior to enrollment in the study.

Study Design and Statistical Analyses

A one-way within-subjects-design was used to perform the study. Two separate baseline measurements were performed one week apart and averaged prior to oxandrolone administration (20 mg/day). Repeat measurements were performed after one month of treatment. Pre- and post-treatment values were compared by a matched sample t-test. The percent change from baseline was calculated and compared to the null hypothesis using a one-sample t-test. A probability of less than 0.05 was considered to be significant. The results are reported as mean±SD.

Pulmonary Function (Spirometry and Maximal Pressures)

Pulmonary function measurements were obtained from subjects while seated in their wheelchairs, using a computerized pulmonary function lab (System 2200, SensorMedics Inc., Yorba Linda, CA). A minimum of three flow-volume loop trials that included the full inspiratory portion of the loop were performed according to the recommendations of the American Thoracic Society (15–17). Spirometry results were expressed as absolute values and the percent was predicted based upon the standards of Morris et al. (18). Forced vital capacity (FVC), forced expired volume in one second (FEV_1), the ratio of FEV_1/FVC, peak expiratory flow rate (PEF), forced inspiratory vital capacity (FIVC) and forced inspiratory vital capacity in one second ($FIVC_1$) were chosen to be analyzed and reported. Respiratory muscle strength was obtained by measurement of maximal inspiratory (PImax) and expiratory (PEmax) pressures, using an electronic portable mouth pressure meter (Vacu-Med, Ventura, CA). Three maximum inspiratory efforts at functional residual capacity and three maximum expiratory efforts at total lung capacity were performed. The best effort for each of the three maximal inspiratory and expiratory pressures were recorded.

Symptoms of Dyspnea

Resting breathlessness was determined by use of the modified Borg dyspnea scale and was self-reported by the subjects before each testing session.

Nutritional Intake

The subjects were instructed by a registered dietitian to eat a minimum of 1 g/kg/day of protein during the course of the treatment month.

Serum Lipid Profile and Liver Function Tests

Blood samples were drawn and analyzed for the serum lipid profile and liver function tests by personnel of the clinical laboratory, Veterans Affairs Medical Center, Bronx, NY. Determinations were performed for total cholesterol, triglycerides, and high density lipoprotein cholesterol (HDL-c), and calculated for low-density lipoprotein cholesterol (LDL-c) [LDL-c = total cholesterol - HDL-c - (triglycerides/5)]. Liver function tests (LFTs) were determined for serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), and lactic dehydrogenase (LDH).

Results

The mean age of the group was 41±9 years (range: 26–51). The subjects had a mean duration of injury of 16±8 years (range: 7–31). The mean height was 1.81±0.07 m (range: 1.73–1.93). Mean weight increased by 2±2% after one month of oxandrolone treatment (76.9±18.3 vs. 78.3±18.9 kg, p<0.05).

As expected in persons with cervical cord lesions, baseline pulmonary function values were significantly reduced from predicted, but measures of spirometry showed significant improvement after one month of oxandrolone treatment (Table 1). Percent change from baseline increased an average of 9.3±2.4 % for the spirometry values combined (Fig. 1).

Baseline values for PImax and PEmax were significantly reduced from those predicted (62±19 and 15±13% predicted) (Table 2). PImax and PEmax significantly increased by an average of 7.3±5.5 cm H_2O and 5.1±7.1 cm H_2O, respectively (Table 2). The percent increase from baseline for PImax was significant (10.2±6.8%, p<0.005), although for PEmax the increase did not reach significance (9.2±13.2%) (Fig. 2). Subjective symptoms of resting dyspnea were reduced by 37±28 percent, a half point reduction on the Borg scale (2.0±2.0 vs. 1.5±2.0, p<0.05).

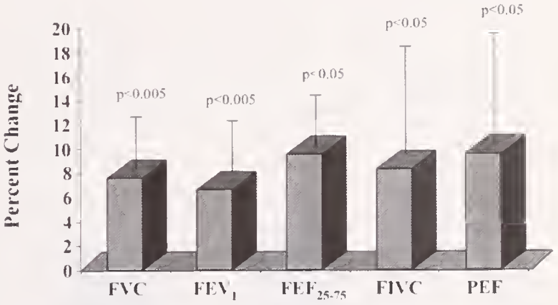

Fig. 1. Percent change in pulmonary function from baseline after one month of oxandrolone treatment.
FVC=forced vital capacity, FEV_1=forced expired volume in one second, FEF_{25-75}=forced expiratory flow between 25 and 75 percent of the FVC, FIVC=forced inspiratory vital capacity, and PEF=peak expiratory flow rate.
p values represent significant change from baseline.

Table 1
Results of Pulmonary Values Before and After One Month of Oxandrolone Therapy

	Baseline L (%pred)	Post-Treatment L (%pred)	Paired Differences L
FVC	2.79±0.95 (53±18)	2.99±1.01 * (57±19) *	0.196±0.167
FEV_1	2.23±0.73 (56±19)	2.36±0.71 * (59±18) *	0.122±0.970
FEV_1/FVC	(83±12)	(83±10)	(<1±5)
FEF_{25-75}	2.39±0.96 (56±23)	2.56±0.94 (59±23)	0.170±0.260
FIVC	2.53±0.90 (47±17)	2.71±0.93 § (49±19)	0.178±0.187
PEF L/sec	4.42±1.53 (45±16)	4.72±1.42 (48±14)	0.307±0.603

Results are reported as mean±SD.
Paired differences=mean values for the post-treatment minus the baseline for each subject.
*p<0.005 and §p<0.05 for baseline versus post-treatment.
%pred=percent of predicted.
FVC=forced vital capacity; FEV_1=forced expired volume in one second;
FIVC=forced inspired vital capacity; PEF=peak expiratory flow rate

Table 2
Results of Maximal Pressures Before and After One Month of Oxandrolone Therapy

	Baseline cm H_2O (%pred)	Post-Treatment cm H_2O (%pred)	Paired Differences cm H_2O
PImax	74±22 62±19	81±24 * 68±20 *	7±5
PEmax	34±29 15±13	39±31 § 18±14 §	5±7

Results are reported as mean±SD.
Paired differences=mean values for the post-treatment minus the baseline for each subject.
*$p<0.005$ and §$p<0.05$ for baseline versus post-treatment.
% pred=percent of predicted.
PImax and PEmax=maximal inspiratory and expiratory pressures.

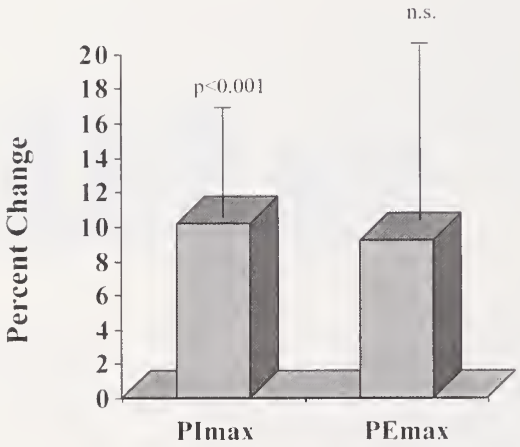

Fig. 2. Percent change in maximal pressures from baseline after one month of oxandrolone treatment.
n.s.=non-significant, PImax=maximal inspiratory pressure, PEmax=maximal expiratory pressure.
p value represents significant change from baseline.

After one month of oxandrolone treatment, liver function enzymes increased slightly from baseline, but remained in the normal range except for ALT, which increased by 2-fold above the upper limit of normal ($p<0.05$). Total cholesterol, triglycerides and LDL-c increased slightly from baseline, but remained within the normal clinical range (150±17 vs. 156±28, 97±47 vs. 81±31, and 89±14 vs. 117±29 mg/dL, respectively). Serum HDL-c decreased significantly by an average of 47% (43±9 vs. 23±5 mg/dL, $p<0.0001$).

The normal values for liver function tests are: ALT < 45 U/L, AST < 41 U/L, total cholesterol < 200 mg/dL, LDL < 130 mg/dL, and HDL > 35 mg/dL.

Discussion

Improvements were noted in both the inspiratory (FIVC and FIV_1) and expiratory (FVC, FEV_1, $FEF_{25-75\%}$, and PEF) portions of the spirometric maneuver. The diaphragm is innervated at C_3 to C_5 and is predominantly used for resting breathing. The intercostals (innervated T_1 to T_{12}) and abdominal wall muscle group (innervated T_7 to L_4) provide respiratory muscle strength for maximal inspiratory and expiratory efforts. With denervation of the intercostal and abdominal wall muscles of respiration, the diaphragm can be recruited for maximal inspiratory and expiratory efforts. Although diaphragmatic size was not measured, the positive changes in pulmonary function are probably explained by an increase in diaphragmatic mass.

Improvements in the maximal inspiratory pressures are consistent with the findings of Annemie et al. (13), in which the effect of an anabolic agent (nandrolone decanoate) combined with nutritional supplementation, and nutritional supplementation alone, and placebo were compared. After 4 weeks of treatment, the nandrolone decanoate combined with nutritional supplementation group and the nutritional supplementation alone group demonstrated significant improvement in PImax compared with the placebo group. However, after 8 weeks of treatment, only the nandrolone decanoate combined with nutritional supplementation group was significantly different from the placebo group. The nandrolone decanoate combined with nutritional supplementation group also demonstrated concurrent improvement in weight gain and fat-free mass (measured by bioelectrical impedance plethysmography). Subjects in our study gained an average of 1.4 kg of weight, albeit body composition was not determined. Oxandrolone has some advantages over nandrolone decanoate. Nandrolone decanoate is administered by intramuscular injection; oxandrolone is an oral preparation. Additionally, nandrolone decanoate has an androgenic-to-anabolic activity ratio of 1:2.5 – 1:4, whereas oxandrolone has much higher anabolic potency (1:3 – 1:13) (19).

Use of the anabolic agent oxandrolone was associated with significant improvement in pulmonary function and subjective rating of dyspnea at rest in subjects with tetraplegia. This improvement is likely the result of increased respiratory muscle mass due to the anabolic function of oxandrolone. Further studies are planned using a double-blind placebo trial to determine the efficacy of therapy. Follow-up after discontinuing treatment, to determine the length of time of a potential beneficial residual effect in pulmonary function, should be considered, as well as the rapidity of return to baseline values of HDL-c levels and LFTs. Chronic use of oxandrolone may not be indicated, due to the adverse changes in serum HDL-c levels. However, the significance of the serum HDL-c change is not clear, given the known suppressant effects of anabolic steroids on lipoprotein a [Lp(a)] levels (20, 21). If HDL-c levels are reduced concurrently with Lp(a) levels, then the net effect for cardiovascular risk may be negligible. If an anabolic agent without the adverse HDL-c complications becomes available in the future, its chronic use in reducing pulmonary complications in persons with tetraplegia may be determined.

In conclusion, oxandrolone may be indicated for individuals with tetraplegia who are nutritionally depleted and have compromised pulmonary function due to pneumonia, atelectasis, bronchial spasms or other such conditions, and who are in need of respiratory muscle strengthening to assist with breathing.

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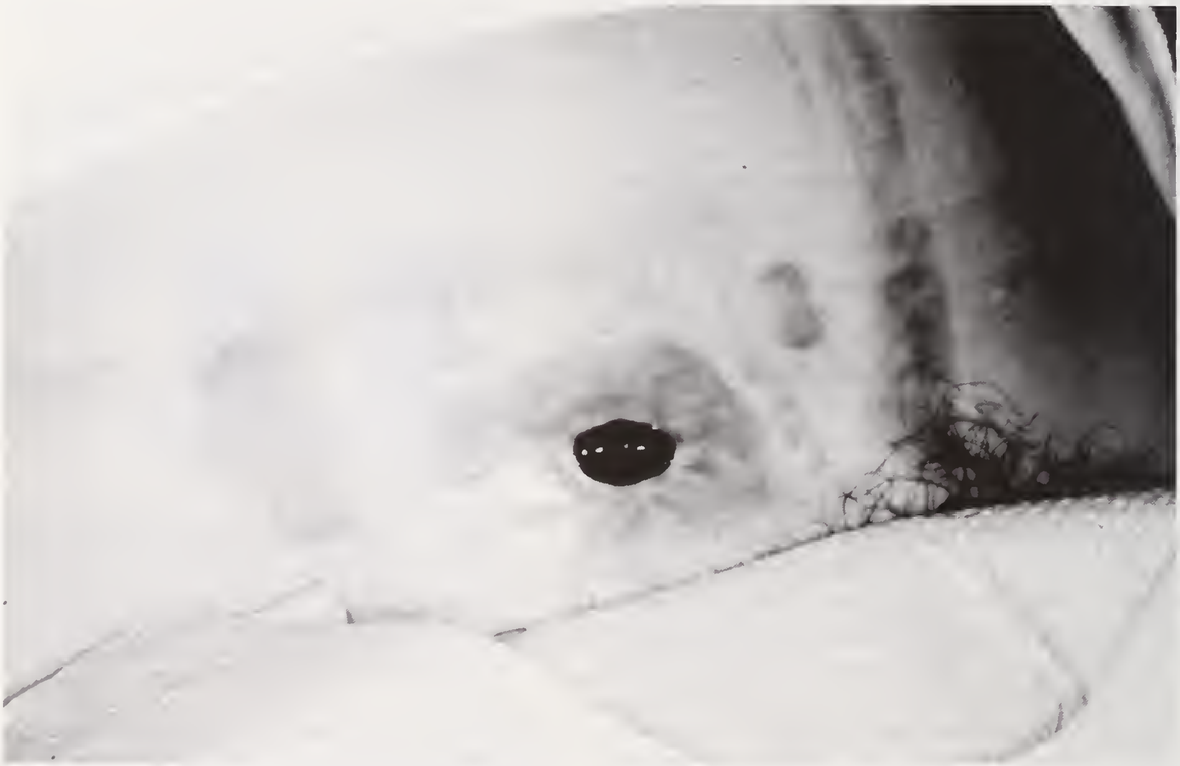
Psoriasis and Crohn's Disease



Peristomal irritation is common, but a sharply demarcated, erythematous scaling plaque in the peristomal area should trigger a search for psoriasis, especially in patients with Crohn's disease. The association between these two disorders is not widely known, but has been reported.

—Donald Rudikoff, M.D., Jacob Baral, M.D., and Mark Lebwohl, M.D.

Letter to the Editor

To the Editor: I read with interest the recent Clinicopathological Conference presenting a patient with constrictive pericarditis (1), and I applaud the reinstitution of this important feature in *The Journal*. However, the discussion contained several inaccuracies pertaining to obstructive sleep apnea syndrome that I would like to correct.

The authors state that "difficulty in sleeping" suggests obstructive sleep apnea syndrome (OSAS), implying that an insomnia complaint should raise suspicion of this disorder. Although it is true that individual obstructive respiratory events typically conclude with electroencephalographic evidence of arousal, these awakenings are usually not remembered by the patient due to their brevity. Obstructive sleep apnea is diagnosed in only a small percentage of patients with an insomnia complaint, averaging only 4.7% in one recent 5-center cooperative study (2). Rather, an insomnia complaint is much more commonly the result of psychiatric illness or of psychophysiological origin (so-called "learned" insomnia).

The authors also imply that shortness of breath is a known consequence of obstructive sleep apnea. Transient dyspnea may sometimes occur in association with nighttime awakenings in the minority of patients who experience sleep-maintenance insomnia from obstructive respiratory events. However, dyspnea at other times is not usually attributable to OSAS, but is more likely a consequence of the obesity that inflicts many of these patients. Obesity is a well-known cause of exertional dyspnea largely because of the increased ventilatory demands imposed by the higher levels of oxygen consumption (VO_2) that occur for any given level of work load in the overweight individual (3). The authors also list abnormal ventilation/perfusion lung scanning as one of the findings in obstructive sleep apnea, but again this finding can be attributed to obesity (due to impaired ventilation of dependent lung units) (4) and is not reported in obstructive sleep apnea alone.

The authors go on to imply that daytime hypercapnia is a frequent complication of obstructive sleep apnea. However, most patients with obstructive sleep apnea syndrome are eucapnic when awake. Estimates of the prevalence of diurnal hypoventilation in obstructive sleep apnea syndrome vary, with published values ranging from 14% to 37% in patients with generally severe disease unselected for degree of obesity (5–7). Patients with OSAS and diurnal hypercapnia tend to be more obese (5–7) and to have coexisting airways disease (5). Daytime eucapnia is achieved in only a subset of patients with OSAS and obesity-hypoventilation syndrome receiving effective treatment for OSAS, indicating that obesity alone is primarily responsible for hypoventilation in some individuals (8). I can find no published report specifically addressing the prevalence of awake hypoventilation in nonobese patients with sleep apnea, but the foregoing considerations suggest that only a small minority will be so affected. Finally, the authors suggest that secondary erythrocytosis is a common finding in obstructive sleep apnea. Polycythemia actually occurs in only a small percent of patients with obstructive sleep apnea (9); the transient episodes of nocturnal hypoxemia that accompany OSAS are usually insufficient to raise erythropoietin levels to a significant extent (10).

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(The above letter was sent to Dr. Michael Kim, who had discussed the differential diagnosis in the original article. A response has not been received.)

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Introduction

Daniel A. Moros, M.D., Rosamond Rhodes, Ph.D.,
and William Fisk, M.A.

Above all, the Hippocratic Oath (1) promises those who suffer from disease that their physicians can be trusted. Long before the contemporary elaboration of bioethical principles for medical practice, physicians appreciated the need for trust in the doctor-patient relationship and the moral necessity of physicians being trustworthy in the use of their special knowledge and skills. And before confidentiality was ever claimed as a right of individual patients and protected against the intrusive power of the state, the Hippocratic Oath made confidentiality a duty of the physician and trustworthiness a virtue of the Hippocratic practitioner:

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>
> What I may see or hear in the course of the treatment or even outside of the treatment ... I will keep to myself, holding such things shameful to speak about.

As medical knowledge has grown and as medical treatment has become more effective, health care providers have become more intrusive in their history taking and more aggressive in their diagnostic and therapeutic interventions. A medical history now routinely includes probing questions about sexual behavior, alcohol and drug use, psychiatric problems, familial and inherited diseases. Information about individuals' health and medical care is collected in patients' records and computerized databases that are shared with a wide range of clinicians, researchers and, with the patients' consent, with insurers and employers. In its traditional sense, as physician Mark Siegler (2) has written, confidentiality may well have become "a decrepit notion." Yet, in the realm of treatment, where patients are subjected to invasive diagnostic procedures, where vital organs are removed and transplanted, and where known poisons are administered as chemotherapy, trustworthiness remains the central virtue of physicians and trust remains a central concern in the practice of medicine.

In a culturally and ethnically diverse society such as ours, the grounds for distrust are inevitably magnified. Health care for the poor is usually provided by physicians who are economically better off than these patients. Health care for patients from racial or ethnic minority groups is usually provided by white physicians who are well integrated into the cultural majority, so linguistic, educational, and cultural barriers may divide patients from practitioners. Some patients do not have adequate access to medical care. And physicians' health care decisions, increasingly dictated by the results of controlled clinical trials, may well clash with the culturally and religiously sanctioned beliefs and practices of the patients.

While the editors of this special issue are not enamored with the welter of alternative medical care modalities currently gaining official respectability, we are acutely aware that competing and incompatible beliefs regarding diagnosis and treatment, as well as their lack of a shared perspective on how to justify medical claims, often make trust difficult in the medical arena.

The thirteenth annual New York Regional Conference on Medical Ethics considered many of these issues in its meeting on "Hope, Distrust and Allocation: Minority Distrust of Medicine." This conference, sponsored by the Mount Sinai School of Medicine and the Ph.D. Program in Philosophy of the Graduate School, CUNY, brought together a multidisciplinary group of physicians, nurses, philosophers, lawyers, and health care advocates to consider the origins and implications of minority distrust of the health care system. Unlike misplaced trust, which may have no immediate impact on care, distrust often limits the ability of patients to seek, and of medical personnel to provide, health care.

Some of the papers from this conference, like those of philosophers Robert Baker, Leslie Francis, Howard McGary, and Laurence Thomas, and of lawyer Kenneth DeVille, offer broad perspectives on the role of trust in medicine, minority distrust and recent governmental and other efforts to correct past inequalities both in providing access to medical education and in delivering health care. Other papers, like those of physician Ian Holzman and philosopher Lance Stell, provide striking vignettes with commentary on distrust within the hospital-based acute-care setting. Still others, by physicians David Schonholz, Lynne Richardson, Cheryl Smith, Milton Wainberg, and Millicent Sutton, nurse Lorna Canlas, and medical students Chen-Li Sung and Christine Kajubi, offer history and commentary on specific groups, e.g., recent Chinese or Latin American immigrants, African Americans, and patients with sickle cell disease. They describe the struggles of individuals from these groups to receive satisfactory care and to develop trusting relationships within our current health care system. As editors as well as organizers of the conference, we hope that this issue of *The Mount Sinai Journal of Medicine* will help encourage discussion about the experience of minority group members in their encounters with the health care system. We also hope that it will highlight the importance of trust in the doctor-patient relationship and alert physicians and other health care providers to the serious damage that can be caused by distrust.

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Minority Distrust of Medicine:

A Historical Perspective

Robert Baker, Ph.D.

Abstract

Recent philosophical work has disclosed a host of problems in our apparently natural ways of classifying things. The contemporary classification of certain groups as "minorities" exemplifies some of these problems. I argue that these classifications are arbitrary and misleading. Through examining several of the most significant ethical moments in the history of modern medicine, including the thought and conduct of Nazi physicians, the Tuskegee study, Beecher's questioning of post-war research practices and Percival's enunciation of a universalist ethic for physicians, I make a case against racial and ethnic classification of patients. Such classifications can play a destructive role in determining the sort of health care which minorities receive. Embracing them, even with the intent of improving the lot of those who do not fare well in the present health care environment, is subversive of the egalitarian stance which has been central to medical ethics since Hippocrates. **Key Words:** Allocation, discrimination, ethnicity, egalitarianism, Hippocratic Oath, history of medical ethics, medical ethics, medical language, minorities, Nuremberg code, Nazi medicine, physician-patient relationship, race, Tuskegee Syphilis Study.

> Everything is what it is and not another thing.
> Bishop Butler, 1729 (1)

> For us, the human body defines, by natural right, the space of origin and distribution of disease; a space whose lines, volumes, surfaces and routes are laid down, in accordance with a now familiar . . . anatomical atlas. But this order of the solid, visible body is only one way—in all likelihood neither the first, nor the most fundamental—in which one spatializes disease. There have been, and will be, other distributions of disease.
> Michel Foucault, 1963 (2)

Words and Things

It is a truism of contemporary philosophy that Bishop Butler's seemingly incontestable claim that "everything is what it is," is wrong (1). Things, even seemingly substantial things like diseases and races, are constructed and sustained as much by conceptual frameworks as by what they are, so to speak "in themselves." In the discourse of American medicine, for example, the term "minority" that appears in the title of this paper is a construct that does not refer to minorities in any literal sense. A computer-generated survey of the use of the term "minority" in hospital and medical journals over the past five years, found not one instance in which "minority" was used to designate White Anglo-Saxon males, or Sephardic Jews, although both are clearly non-majority populations. The term was characteristically used to identity three specific minorities who collectively represent 22% of the American population: African Americans, Latinos and American Indians. A review of the medical literature establishes that this usage became prevalent in the 1980s. During that period the government declared it a "national health goal . . . to reduce disparities in the health of members of racial and ethnic minority groups"—specifically, differences between the health of the three groups in question

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and that of "non-minority" populations, that is, everyone else (3). This use of the word "minority" seems to have originated in part as a euphemism for the term "race," a "four-letter word" often avoided in polite medical or scientific discourse.

Generally implicit (and often explicit) in the 1980s substitution of the term "minorities" for the expression "racial or ethnic minorities" are the presuppositions that these "minorities" have poorer health status than non-minorities, that they have this status because they "receive the fewest health services" (4) and that "racial and ethnic minority populations make up a disproportionate percentage of the medically underserved" because they are vulnerable to racial and ethnic discrimination. Thus the expression "minority" in the medical literature is typically used to indicate African Americans, Latinos, and Native Americans because these three groups are presumed to be medically underserved as a result of racial and ethnic discrimination. To document these presumed inequalities in health status and in access to health care, from the mid-1980s onwards, the National Center for Health Statistics and the U.S. Department of Health's Taskforce on Black and Minority Health began systematically to collect and publish comparative data using ethnic and racial categories (5, 6). In these comparisons, the term "minority" was typically used to designate "medically underserved ethnic and racial segments of the population who are vulnerable to discrimination" (MERV).

In February 1998 the Clinton administration, acting on the basis of over a decade of MERV comparison data, proposed a $400 million campaign to wipe out ethnic and racial differences in health status. "Nowhere are the divisions of race and ethnicity more sharply drawn than in the health of our people," President Clinton proclaimed, citing MERV comparisons such as those showing that black children are two and a half times more likely to die in infancy than are white children. In commenting on the President's proposal, Health and Human Services Secretary Donna Shalala remarked (7) that the race-based initiatives were needed because "we can't wait for everybody in the country to get good health insurance"—implying that the proposed MERV-based initiative was an alternative to the administration's failed attempt to secure universal health insurance.

As Leslie Francis has astutely observed (8), the Clinton initiative presumes a civil rights reading of the MERV comparison data, that is, it presumes that this data documents a legacy of racial discrimination in American health care, and it proposes to rectify this problem through an affirmative action initiative.

In this paper I shall argue that: (1) MERV comparisons are problematic because they obscure the dominant pattern of minority and majority convergence with respect to health-care status; (2) even if the data were reliable, the mere fact that we can construct such comparisons does not demonstrate ethnic and racial discrimination; and (3) even were there, in fact, significant ethnic and racial discrimination in American health care, the proposed "civil rights" remedy instills ethnic and racial categories into medical language and thought, and by doing so is potentially more dangerous to "minorities" than alternative approaches to health-care reform.

The Problematic Nature of MERV Data: Grueishness

Over the course of this century, the dominant trend documented by health statistics is that disparities between all ethnic and racial groups are diminishing. Thus the National Center for Health Statistics Year 2000 reports (5) that, whereas in 1900 life expectancy for whites was 47.6 years, compared to a life expectancy for blacks of 33.0 years, by 1990 life expectancy was 76.1 years for whites and 69.1 years for blacks. The data thus reflect extraordinary gains in life expectancy for blacks, whose lifespan has more than doubled since 1900; by comparison, the lifespan of whites has only increased by about 50%. Yet, since the stated objective of MERV comparisons is to document ethnic and racial health-care inequality, most MERV comparisons focus on differences in excess deaths for individuals younger than 70 years old in minority as compared to majority populations. Since the average lifespan for blacks, at 69.1 years, is under 70, while that for whites, at 76.1 years, is over 70, these analyses emphasize inequalities. What they reveal, not surprisingly, is that in comparison to whites, blacks experience an impressive-sounding 42.3% excess of deaths, Native Americans a 25% excess, the Spanish-surnamed population of Texas a 14% excess, Mexican-born Americans a 14% excess, and Cuban-born Americans a 2% excess. Yet, to reiterate, in emphasizing that blacks suffer a 42.3% excess of deaths over whites, the data obscure the dominant trend of converging lifespans in all American populations.

The aim of highlighting ethnic and racial disparities in MERV comparisons sometimes leads statisticians to create odd comparison categories, such as the "white mothers of Chinese, Japanese, Filipino, Cuban and non-Hispanic descent" category used by the National Center for Health Statistics (5).

> As in 1980, about a quarter of the women who gave birth in 1990 failed to receive prenatal care in the first 3 months of pregnancy. Differences existed by race and Hispanic origin in the percentage of mothers who receive prenatal care early. In 1990, only about 60 percent of Hispanic (except Cuban), American Indian, and non-Hispanic mothers received care in the first trimester. Early prenatal care reached about 80 percent *among white mothers of Chinese, Japanese, Filipino, Cuban and non-Hispanic descent.* Unmarried or teenage mothers were the least likely to receive timely prenatal care. [italics added]

As the italicized terms indicate, in this particular MERV comparison mothers of Cuban and Asian American descent are construed as "white." It is noteworthy that, as members of a minority come to have the same health status and access to health care as do white mothers, they are called "white mothers," thereby heightening apparent differences between minority and "white mothers," even though, in fact, actual differences have been diminishing.

In reality, of course, Chinese Americans, Cuban Americans, German Americans, Italian Americans, Japanese Americans, Jewish Americans and Filipino Americans are distinctive groups, and Cuban, Chinese, Filipino and Japanese mothers would be startled and perhaps amused to discover that they were really white. To anyone familiar with the technical tools of analytic philosophy, this anomaly suggests "grueishness." "Grue" is the category of all things that are either observed before a certain date and green, or observed after that date and blue. This concept was invented by the American philosopher, Nelson Goodman. He constructed it to demonstrate that a logically or statistically valid category may divide the world in a capricious way that is useless for getting knowledge. In this way, the category "grue" is arbitrary and serves no explanatory function. To say that an item is "grueish" is thus arbitrary and useless. By the mid-1990s many researchers were beginning to suspect that MERV comparisons, insofar as they involve statistics lumping "mothers of Chinese, Japanese, Filipino, Cuban and non-Hispanic descent" into a single category, "white," were decidedly "grueish" artifacts of the statistician's imagination.

The Case Against MERV Comparisons

As the French philosopher Michel Foucault has observed (2), there are many ways of categorizing "health" and "disease." The deepest question raised by MERV comparisons is whether we wish to construct public health surveillance data in terms of ethnic and racial categories. Do we really wish to train every medical student, intern, resident, fellow, and attending physician to classify each and every patient in ethnic and racial terms?

The case against MERV classifications coalesced in the workshop "On the Use of Race and Ethnicity in Public Health Surveillance" sponsored by the Center for Disease Control (CDC) in January 1994. In a paper on "The Concept of Race and Health Status in America," David Williams, a sociologist from the University of Michigan, Risa Lavizzo-Mourey of the Public Health Service, and Rueben Warren of the CDC contended (9) that collecting data using racial categories not only promotes thinking in "racial stereotypes," it reinforces the outmoded presumption that "race is a valid biological category." More specifically, they pointed out that

> Although widely shared in our society, the belief that races are human populations that differ from each other primarily in terms of genetics is without scientific basis. There is more genetic variation within races than between them and racial categories do not capture biological distinctiveness . . . . Racial taxonomies are arbitrary. . . . race is more of a social category than a biological one (9).

Williams and associates argue that yet another problem with "race-based" data collection is that it often masks truly causative factors, such as geographical and socio-economic factors. Sickle cell disease, for example, is more accurately conceptualized as a geographical rather than a race-based disease.

> Although more common in blacks [sickle cell trait] appears not to result from race, but from geographical origin. Sickle cell disease occurs in white populations both within and outside the United States. The disease is most prevalent in the regions of the world where malaria was common

> (equatorial Africa, the Mediterranean, and parts of Asia) and appears to be a protective adaptation to malaria (9).

Race-based categories may also mask the effects of socio-economic status (SES):

> One of the most established patterns in social epidemiology is the relationship between SES and health. Persons with high levels of income, education, or occupational status live longer, and have lower rates of disease than their counterparts of lower social [-economic] status . . . . When racial disparities in health status are adjusted for SES, racial differences are substantially reduced and sometimes eliminated (9).

In the June 4 and July 2, 1997 issues of the *Journal of the National Cancer Institute*, key members of the President's Cancer Panel also protested that the focus on MERV comparisons masks the impact of SES. Nancy Krieger of the Harvard School of Public Health said, as reported by Reynolds (10), "that blacks, for example, have a median net worth only one-twelfth that of whites," and that "in 1991, in the lowest income quintile, the median net worth of white households was $10,257, while in black and Hispanic households it was $1.00 and $645." It also was indicated by the panelists that the absence of attention to such socioeconomic data continues to fuel erroneous notions that race is "biologic," and that we need to understand race in that way, or in purely cultural terms, and not take into account the effects of socioeconomic positions and gaps in income and wealth in this country (11).

Other authorities assembled by the President's Cancer Panel worried about a different and in many ways more important point: that the need to assemble data in racial terms introduced unscientific ethnic and racial stereotypes into the supposedly scientific literature. Solomon Katz, of the University of Pennsylvania (10), stated bluntly that "the biological category of race as applied to humans has no legitimate place in biological science." Dr. Harold Freeman (10), of the Harlem Hospital Center, President of the President's Cancer Panel, observed that "scientists who are well trained today are writing papers in the scientific literature which seem to make the assumption that race does exist, and even may make assumptions about what race is, which are not correct . . . If you make a wrong assumption and start from there your syllogism is off."

It is important to differentiate the several criticisms being voiced here. The primary criticism is that the MERV data are inherently unscientific, since there is no clear methodology for classifying persons as African American, or Latino. Is a Nigerian or a West Indian who is a naturalized American citizen an African American? One answers differently if one identifies African Americans as an American subculture, or as a racial classification. How are persons of mixed race, such as the golfer Tiger Woods, to be classified? As James Davis (11, 12), author of *Who is Black?* has argued, our present system of racial classification, in which "one drop of black blood makes you black, was invented in the 17th century to ensure that children of mixed race would remain slaves." In the modern medical context this classificatory schema means that someone is considered "black" if they either appear black to some health provider, or if they choose to identify themselves as African American on a form filled out on some occasion. This is hardly the stuff of modern genetics. And what of Latinos? Are they all the same irrespective of their country of family origin, the color of their skin, or their proficiency in English? And, to raise the more fundamental question, are researchers gathering data about cultural or subcultural identification, or about skin color? The categorization is unlikely to be anthropologically or genetically sophisticated.

Do the Data Justify Affirmative Action in the Allocation of Health-Care Funds?

Despite the problematic nature of MERV comparisons, many commentators presume that they document real ethnic and racial differences, and demonstrate the effects of institutionalized ethnic and racial biases. To quote from an article in *Pediatrics* by Dr. Aaron Shirley (13), "even when other factors are controlled for . . . the race and ethnicity of patients had a measurable, and limiting, effect on the health care they receive." President Clinton seems to share this belief, since otherwise his proposal for ethnic and racially based civil-rights-style health reform initiative would make little sense. Professor Francis offers an ingenious defense of the Clinton initiative. Francis cites studies that seem to document that blacks are less likely to receive bone marrow transplants, bypass surgery, glaucoma treatment and hip arthroplasty than are whites. Francis argues that since these studies provide strong prima facie reasons to suspect racial discrimination, we are morally obligated to presume discrimination until we find out that some non-discriminatory factor explains the differences—just as we would be in cases involving employment discrimination. Hence, Francis concludes, in the absence of evidence demonstrating non-discrimination, we are obligated to support a civil-rights-style health reform, much like that proposed by the Clinton administration. (See the paper by Leslie Francis in this issue [8].)

This intriguing argument requires us to accept that, even though the purported differences in access to treatment might ultimately be attributable to socio-economic, cultural or subcultural differences that might, for example, make African Americans, Latinos, and Native Americans more distrustful of medical recommendations for aggressive technological medical interventions than people from other American subcultures, we should nonetheless treat data consistent with ethnic or racial discrimination in health-care delivery as demonstrating such discrimination. Francis is thus proposing that we should exempt the theory that the basis of differential health-care outcomes is racism, from the careful and skeptical scrutiny generally accorded causal claims. This exemption is justified, Francis argues, because the need to correct civil rights abuses is so compelling that even a prima facie case for discrimination suffices to justify a corrective policy. Francis notes, moreover, that there is precedent for such an exemption in civil rights law, as is evident from four cases of employment discrimination. In the cases she cites, the courts have held that differences in outcome alone could be treated as presumptive evidence of racial discrimination. Analogously, Francis argues, the reported ethnic and racial differences in health outcomes are sufficient to justify an affirmative action program for health care.

Francis's case for an exemption rests on an analogy between health-care delivery and employment. It thus presumes that the health provider-patient relationship is, in relevant respects, analogous to the employer-employee relationship. Yet there are significant disanalogies between these relationships. Employers pay employees, whereas it is just the opposite in health care: patients, or their insurers, pay health-care providers. Employment discrimination thus does not cost an employer money and it may well increase the paychecks of union members by decreasing the size of the labor pool. For health-care providers, however, every bone marrow transplant foregone by African Americans, every bypass surgery not undertaken, every glaucoma treatment and hip arthroplasty declined means a direct financial loss for the health-care providers involved (except under certain managed care contracts). Discrimination hits health-care providers where it hurts, at the bottom line. Money can thus function as an equalizer in health care but not in employment. Therefore, it is more reasonable to expect bias to be operative in employment than in health care.

Money, however, can only counteract bias when the objects of bias control it. This analysis thus suggests that ethnic and racial bias in health-care delivery is most likely in those areas of medicine over which patients have the least economic control. If this suggestion is correct, then Clinton-like programs, in which minority members themselves do not directly control the funds spent on their behalf, are unlikely to correct ethnic and racial biases in health care. The most effective way to eliminate such discrimination in health care would be economic empowerment of the poor (who are disproportionately African American, Latino, and Native American). For example, giving the poor vouchers enabling them to purchase health insurance from competing managed care organizations would eliminate differences in health-care purchasing power. Managed care organizations would then have every incentive to market products designed to meet the socio-cultural, ethnic, racial and class sensibilities of all Americans, whether their ethnic origin is African, Asian, Latino, Native, or White-Anglo-Saxon-Protestant.

There is a second and equally important lack of analogy between the employment data and the health-care data. Francis cites (8) several cases in which African American employees were disproportionately assigned less desirable, lower-paying jobs. It is reasonable to presume that all employees would prefer more desirable, higher-paying positions, but there is no comparable, reasonable presumption in the health-care cases cited. It is not reasonable to presume that all American subcultures desire aggressive, high-tech medical interventions equally. African, Asian, Latino and Native Americans often accept alternative medical traditions that may make them distrustful of hospital-based high-tech medicine. Thus, if one truly accepts the multiculturalism of American society, one must also accept the right of some American subcultures to be more suspicious of aggressive, high-tech medical interventions, and therefore to accept them at a lower rate, than other subcultures.

There is a pragmatic dimension to the Clinton administration's proposal and to Francis's justification of the policy. American culture developed in the context of more than three centuries of slavery, followed by a century of legally codified racism. Insofar as the data suggest that this tradition may still be influencing American health care, it seems reasonable for Clinton officials to contend that, simply as a practical matter, funds directed at remedying this imbalance might help, and could not be harmful.

In the rest of this paper, however, I will argue that this proposal is potentially harmful because it undermines the Enlightenment-based universalism of modern medical ethics by training physicians to think of their patients in ethnic or racial terms, rather than simply as patients who have different ethnic-cultural and socio-economic backgrounds. This argument rests on a third difference between the employer-employee relationship and the health-care provider-patient relationship. Traditionally, prior to affirmative action laws, employers were held to have some moral responsibilities toward their employees, but they were not held to have moral responsibilities toward potential employees, that is, toward people who were merely job applicants. In modern medical ethics, by contrast, health-care providers have always been held to have a responsibility toward acutely ill persons during medical emergencies—even if they are not yet "patients."

In America, this responsibility was first stated in the New York Midwives Oath of 1715 (14). It was reiterated with respect to physicians by the New Jersey Medical Society, the first permanent American medical society, in its Instruments of Association of 1766 (15), which states that since physicians have "an office of benevolence and charity, we will always most readily and cheerfully, when applied to, assist gratis, by all means in our power, the distressed poor and indigent." A similar provision was retained in the American Medical Association's 1847 Code of Ethics (16), "Poverty . . . should always be recognized as presenting valid claims for gratuitous service . . . [which] should always be cheerfully and freely accorded" (16). Even today, despite the commodification of health-care services, every emergency room in every hospital in America opens its doors to anyone in need of acute care services, irrespective of their ability to pay. Employers have never undertaken a comparable moral responsibility for job applicants.

Medicine's duty to treat the acutely ill is but one aspect of a rich moral tradition of beneficent egalitarianism toward patients. This tradition also tends to protect patients against discrimination. Historically, patients have become vulnerable to socio-economic and/or ethnic and racial discrimination in medicine only insofar as they have been exempted from these traditional protections. In the next section I review some of the linguistic-conceptual mechanisms by which patients have been denied protection and made vulnerable to discrimination in previous eras of Western medicine. I will argue that the system of ethnic and racial classification required to implement any Clinton-Francis style initiative would also undermine the moral protections traditionally enjoyed by patients.

The Tradition of Beneficent Egalitarianism in Western Medical Ethics

The medical ethical tradition of beneficent egalitarianism toward patients, like Western medicine itself, was invented by the Greeks roughly two and a half millennia ago. One of the earliest and best-known formulations of ancient medical ethics is the Oath attributed to Hippocrates. Scholars have differed on the importance of the Oath. Until recently most scholars followed the lead of Ludwig Edelstein in holding that, despite the Oath's influence on posterity, it was relatively unimportant to physicians in the ancient world (17–19). Recent work by Owsei Tempkin (20) and Hendrick van Staden (21) has successfully challenged this view, and the Oath has been restored to its place as the single most important text in the history of Western medical ethics, from ancient times to the present day.

Two lines in the Oath's code of conduct relate directly to the question of the treatment of minorities: "I will use treatment to benefit the sick according to my ability and judgment, but never with a view to injury or wrong-doing"; "Into whatsoever houses I enter I will enter to help the sick, and I will abstain from all intentional wrongdoing and harm . . . especially from abusing the bodies of man or woman, bond or free." The Oath thus requires that all persons treated by a physician receive treatment intended for their benefit, irrespective of their status as male or female, slave or free. This core Hippocratic notion, that all sick persons are to be treated and respected equally, created an island of egalitarianism in a world that then, even more than now, was notorious for its inegalitarian treatment of ethnicity, gender, race, socio-economic class and status.

The egalitarianism of the Oath was reinforced with the rise of Rome, as Greek physicians tried to earn a living by practicing their medical skills on their Roman conquerors. To reassure his patrons that his medicines were not "poisons," the 1st-century Greek physician Scribonius Largus assured his patrons that:

> No man bound by the medical profession [i.e., the Oath] will give dangerous drugs to anyone, even to enemies of the state, although, when events demand, the same physician will fight against them as a soldier and good citizen with every means at his disposal. This is because Medicine truly promises her assistance in equal measure to all who seek her aid, and she swears never to injure anyone deliberately, for she judges men neither by their fortune nor their character. Hippocrates, the founder of our profession, handed down to our discipline an oath . . . [in which] Medicine is the science of healing, not harming (22).

In era after era, it served physicians well to reaffirm the traditional beneficent egalitarianism of the Oath. Even in the 18th century, when the Oath was supplanted by an ethics of professional morality, professional medical ethics retained this core Hippocratic value. Thus Thomas Percival (1740 – 1804) (23), who coined the terms "medical ethics" and "professional ethics," rephrased the Hippocratic ideal of beneficent egalitarianism in the new language of "medical ethics" when he asserted that "Every case, committed to the charge of a physician or surgeon, should be treated with attention, steadiness and humanity" (23). This line is a line echoed, almost word-for-word, in the foundational document of American medical ethics, the 1847 American Medical Association's Code of Ethics, (Chapter I, Article I, Section II [16]).

Conceptual-Linguistic Marking and Discriminatory Practice

Minorities are clearly protected by the beneficent egalitarianism that lies at the core of the Western medical ethical tradition. One might presume, therefore, that at least at the level of ethical principle, the history of minorities in Western medicine is a history of beneficent egalitarianism, and that the conduct of medical practitioners could thus serve as a model and a rebuke to the rest of society. Would that history were so straightforward. One might think that, to quote Bishop Butler (1), "Everything is what it is and not another thing," and so all sick people would be treated as sick people, and thus protected equally by the traditional ethic of beneficent egalitarianism. Historically, however, people have invented clever ways of distinguishing between apparently identical things, and have used these distinctions to discriminate. One way in which they do this, linguistically, is by "marking" nouns to differentiate subsets from the class of objects or persons normally picked out by the noun. For example, a "woman driver" is not merely a driver who happens to be a woman, as is evident from the fact that we have no correlative expression "man driver"; rather, the expression marks women as different from, and presumably inferior to, the normal driver, who is presumed to be a man. Other similar uses of "woman" mark out women as unusual, different from what the speaker would normally expect: "woman doctor," "woman golfer," "woman surgeon," and so forth. In each case, the marked form designates a non-normal and presumptively inferior subclass. The mechanisms for marking may also attach to suffixes, as it does in the term "poetess," for example. Here again, the marked form implies both differentiation and inferiority (21).

One notorious use of noun marking occurred in 1938. Heinrich Rothmund, a Swiss police official, feared that the Swiss would be subjected to *Überfremdung* (ethnic contamination) from the flood of Jews fleeing Nazi Germany, because all holders of German passports could enter Switzerland without a visa. To remedy this "problem" Rothmund requested that the German government mark the passports of all Jewish citizens with a "J" to distinguish them from other German citizens. The Germans agreed, provided that the Swiss government reciprocate. Soon both governments began to mark the passports of their Jewish citizens with a "J", thereby transforming citizens who happened to be Jews into "Jewish citizens." Linguistic marking soon translated into discriminatory practice and "citizens" with marked forms soon found that they had lost the right to cross the German-Swiss border (25).

Another linguistic distinction with morally disturbing consequences was prevalent in the medical language used in Britain two hundred years earlier. Eighteenth-century Britain was the birthplace of the modern hospital, which was originally thought of as a charitable institution that specialized in aiding sick persons. Perhaps not unnaturally, therefore, sick persons treated in hospitals were always referred to as "sick poor," never as "patients"—a term that was reserved for upper- and middle-class private practice patrons. Although these linguistic distinctions seem trivial, they had substantial consequences. Patients were accorded confidentiality and all the other traditional protections afforded by a beneficently egalitarian Western medical ethical tradition. (This was not a particularly altruistic policy, since the socio-economic status of upper-class patrons was typically higher than that of their physicians.) By contrast, the sick poor were treated as being in all ways less deserving, and were denied confidentiality and other traditional ethical protections. The linguistic distinction between "the sick poor" and "patients" thus enabled physicians and surgeons to maintain a lower standard of conduct toward the "sick poor" while still embracing the tradition of beneficent egalitarianism toward their "patients" (26).

Philosophers are often accused of paying too much attention to mere "words." Yet words designate concepts and concepts structure our world. What, after all, is a hospital but a concept made concrete by brick, mortar, and social practices? In the 18th century, the conceptual division between "patient" and "sick poor" was made concrete in a double standard of treatment. To tear down this double standard, 18th-century medical reformers, like Thomas Percival, had to coin a new language in which the term "patient" was extended to embrace everyone in need of care, "the sick poor" as well as affluent "private patients." In 1794, Percival penned what is perhaps the most radical line in the history of Western medical ethics when he wrote that "the moral rules of conduct, prescribed toward hospital patients should be fully adopted in private practice" (Medical Jurisprudence, Section Two, Article I [27], repeated in Medical Ethics, Chapter Two, Article I [23]). This line precedes the more commonly quoted sentence, "Every case, committed to the charge of a physician or surgeon, should be treated with attention, steadiness and humanity." In these lines, Percival tore down the walls separating "the sick poor" from "patrons," deghettoizing standards of medical practice by insisting that a single term "patient," a single ethic, beneficent egalitarianism, and a single standard of conduct apply to all persons, rich or poor alike (28). In the 19th century, especially in America, these egalitarian precepts became the received canon of medical ethics, adopted in principle, if not always in practice (16).

The Ghettoization of Medical Language in Germany in the 1930s and 1940s

Medical ethics was strikingly reghettoized by the German medical profession during the 1930s and 1940s. Again, linguistic change, conceptual ghettoization so to speak, served as a precursor to physical ghettoization, as ideas of eugenic purity (*Rassenhygiene*) were made concrete as concentration camps and crematoria. As Michael Burleigh, Robert Proctor and others have argued persuasively, the comforting view that German physicians were largely innocent in the affairs of the Third Reich, or that they were corrupted into complicity, or that they were coerced into cooperation with the Nazis, is inconsistent with the known evidence (29–31). Physicians themselves created many of the concepts later adopted by the Nazis, and many physicians were drawn to the Nazi party in its early days because it embraced eugenicist-naturalist-collectivist biological models that they and their teachers had invented. Many German health reformers held that traditional individualist medicine should be supplanted by a "people's health movement" (a movement from *Fürsorge* to *Volksfürsorge*). In this new people's health movement, the older medical obligation to use treatment to benefit the patient was to be transformed into the obligation to serve public health (*Gesundheitspflicht*), a duty understood as preserving racial-cultural community (*Volksgemeinschaft*). The duty to preserve the public health required teaching hygiene and sanitation, developing a communal regimen of fresh air, exercise, and wholesome natural food, and campaigning against habits, such as the use of tobacco, that debilitated public health. Similarly, the duty to preserve racial community required protecting the community against those who posed a eugenic threat to the community (*Gemeinschaftfremde*), and those who could no longer live a life that could meaningfully contribute to the community (*lebensunwerten Lebens*). Racial hygiene involved genetic quarantine through sterilization and the physical elimination of "life unworthy of life." The hygienic killing began with the mentally and physically handicapped, and culminated in the attempt to "purify society" of Jews, Gypsies, and homosexuals.

At the end of World War II, some of the physicians involved in these efforts were placed on trial at Nuremberg. Dr. Karl Brandt, Hitler's personal physician and a key figure in the eugenic extermination program, was asked whether his conduct could be reconciled with the Hippocratic Oath, that is, with the Western tradition of beneficent egalitarianism. Brandt replied that had Hippocrates lived in Germany in the 1930s, he would have revised his Oath. In fact, that is precisely what the German medical profession did: they revised the traditional medical ethics of beneficent egalitarianism by differentiating, first at the level of language and concept, and then at the level of institutional and personal activity, between patients, and *Gemeinschaftfremde* and *lebensunwerten Lebens*. Physical ghettoization lagged behind conceptual ghettoization by several decades. Eventually, however, differentiating concepts were made concrete in concentration camps and crematoria (32).

The Presumption of Nazi Exceptionalism: Some Historical Reflections

The German experience under the Nazis is almost always dismissed as so extreme, so unlike anything that preceded it, that it lacks precedential value. In one respect, however, it is remarkably similar to the pattern we observed in 18th-century Britain. For while there was no holocaust in 18th-century Britain, there was pervasive discrimination against the "sick poor." British physicians reconciled their discriminatory conduct with the traditional medical morality of beneficent egalitarianism by linguistically and conceptually differentiating between patients proper and those whom they treated differently. In Britain, as in Germany, institutional and physical discrimination accompanied linguistic-conceptual differentiation. This said, many would suggest that the disanalogies between the British and the Nazis seem so vast that these few similarities have no precedential value. Yet the belief in Nazi exceptionalism also has a disturbing history. At the Nuremberg trial, in an effort to justify their verdict, the Tribunal issued its now-famous ten principles of morally permissible experimentation on human subjects (29). These principles asserted, for the first time in Western medicine, that the primary requisite of ethically permissible experimentation on humans is the informed voluntary consent of the subject. After the trial ended, there was an attempt to institute the Nuremberg code world-wide. American physicians, however, rejected the code. To justify this, they cited Nazi exceptionalism. "These codes [are] necessary for barbarians but [not] fine upstanding people" remarked one physician ([33], p. 86). Historian David Rothman observed that "The events . . . at Nuremberg were not perceived by researchers . . . to be directly relevant to the American scene . . . the violations had been the work of Nazis, not doctors; the guilty parties were Hitler's henchmen, not scientists . . . . Madness not medicine was implicated at Nuremberg . . . the prevailing view was that [the defendants] were Nazis first and last; by definition nothing they did, and no code drawn up in response to them, was relevant to the United States" (34).

Post-Nuremberg Discrimination Against Research Subjects in the United States

In the early 1960s, perhaps the strongest opponent of the Nuremberg principles was Dr. Henry Beecher of Harvard. In particular, Beecher was opposed to imposing the consent requirement on patients. In therapeutic contexts, he argued, obtaining informed consent was "folly . . . . Difficult . . . to the point of impossible." The patient-subject was best protected by the "character, wisdom, experience, honesty, imaginativeness and sense of responsibility of the investigator" (33). By the mid-1960s, however, Beecher came to the horrifying realization that the Nazi conduct was not as exceptional as he had initially thought. Researchers in American were abusing their responsibilities to those patients whom they were recruiting as subjects. In a process memorably portrayed by David Rothman, Beecher "blew the whistle" on American medical researchers in an article published in the *New England Journal of Medicine* (35). The article analyzed the treatment of human subjects reported in twenty-two research papers published in such leading medical journals as *Circulation, Journal of the American Medical Association* (JAMA), *Journal of Clinical Investigation*, and the *New England Journal of Medicine* between 1948 and 1965. All the papers reported practices in violation of the Nuremberg code. Moreover, if one reviews the papers cited by Beecher, the pattern of conceptual-linguistic differentiation that we observed in the 18th century, and in the Germany of the 1930s and 1940s was sustained. The studies not only target their research at socio-economically, ethnically, racially, and other gender-vulnerable groups—recruiting subjects who were either African American, or Jewish American, or poor, or uneducated, or post-reproductive females, or prisoners, or the mentally handicapped—they refer to their subjects in a language that marked them as different from ordinary patients.

Linguistic Marking in the Tuskegee Syphilis Study

The relationship between linguistic differentiation and unethical treatment is evident, for example, in the most notorious study conducted in the pre-regulatory era, the Tuskegee Syphilis Study (36). The origins of the study trace back to a well-intentioned effort in the 1920s when the United States Public Health Service (USPHS) joined forces with the Julius Rosenwald Foundation of Philadelphia in a project to eradicate syphilis in medically underserved populations. Using race-based categories, the USPHS, acting in cooperation with the Tuskegee Institute, surveyed Macon County, Alabama, and found that 36% of the "Negro" male population had syphilis.

The foundation then planned and began to fund a demonstration project in which 3,694 "Negro" men were to receive treatment with neosalvarsan—the treatment of choice in the pre-antibiotic era. In 1929 the stock market crashed, and mid-project the Foundation found itself without funds. The USPHS also lacked the funds needed to continue providing treatment; nonetheless, it continued race-based surveillance and, in 1931, resurveyed the county and located 399 "Negro" males with untreated syphilis, who were also, as it happened, too poor to pay for medical treatment. This discovery led the USPHS to launch a longitudinal study of "300 syphilitic Negro males who had never received treatment" (37). In order to track this group, the subjects were invited to receive "treatment" for "bad blood" that was "free of charge," although, in fact, they did not receive treatment but were monitored through the use of spinal taps. These observations continued despite the availability of cheap and effective antibiotic therapy in the post-war period. The subjects were never informed that they suffered from syphilis. The study was terminated in 1972 after Peter Buxton, a whistleblower in the CDC, brought the story to the attention of an Associate Press reporter.

Tuskegee and Proposals for Ethnic and Racial Allocation of Health Resources: Some Analogies

Tuskegee, in conjunction with the other research scandals, created a national outcry. A number of investigative committees were formed. One of these, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, adopted a modified version of the Nuremberg code that was to be enforced by institutional review boards. (This form of patient protection was first proposed by Percival in 1794.) Since the initiation of these "new" forms of ethical constraint, the blatant research abuses of the pre-regulation era appear to have been eliminated. We can once more feel complacent about our own decency and dismiss the past as prologue, rather than regarding it as precedent.

Today, confident in their purity of purpose and good intentions, government officials again propose systematically to distinguish African Americans, Hispanic Americans, and Native Americans, from all other Americans in matters of health care. Like the Rosenwald Foundation in the 1920s, the Clinton Administration is offering new money to address pressing health-care needs; like the USPHS in the 1920s, the Department of Health and Human Services is proposing to allocate these funds to medically underserved, racially defined populations. Just as in the 1920s, there will be a temporal limit to the new money that will be expended. Yet, as in the 1920s, the racially constructed surveillance of patients and populations is likely to continue, even after funding sources dry up. No one can tell whether these racially constructed conceptions, like those constructed by the USPHS in the 1920s, will provide a basis for new forms of discrimination. One can be certain, however, that linguistic-conceptual differentiation has served as a springboard for discrimination in the past. Thus, attractive though it may be to target funds at medically underserved, ethnically or racially defined populations, if the past provides a precedent, those populations would be better served were these funds allocated simply in terms of medical need. To paraphrase the most venerable lines in Western medical ethics, funds should be allocated "to benefit the sick . . . whether man or woman, bond or free," black or white, minority or majority.

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Trusting Under Pressure

LAURENCE MORDEKHAI THOMAS, PH.D.

Abstract

This essay explores the idea that it is possible for a patient to feel ill at ease with a health care professional, even though there is no active ill will on the part of the professional. Noting that the relationship between the patient and the health care professional, especially in the case of the physician, is an asymmetrical one, I suggest that it is incumbent upon professionals to take extra steps to insure that the patient feels at ease in the staff-patient encounter, notwithstanding the good will that health professionals may be assumed to have toward patients generally. **Key Words:** Good will, ill at ease, active ill will, trust, hypertension, minority distrust.

NOTHING MAKES ONE PERSON MORE VULNERABLE to another than the absence of power. And nothing makes trust a more indispensable good than the absence of power. In important respects, the relationship between patient and health practitioner involves, as I shall specify below, a power differential which greatly favors the health practitioner. For this reason, the practice of medicine is a playing field for the virtue of trust. The absence of patient trust in the health practitioner may often be a factor when a patient feels ill at ease in an encounter with a nurse or a physician. My main concern in this essay is to show that rendering a patient ill at ease can be compatible with having generalized good will towards others. Indeed, just having good will toward others cannot achieve full equality for all members of society. Evil is opportunistic and does not require active ill will in order to bear fruit.

In the final section of this essay, I speculatively apply the considerations of the first two sections to the case of blacks and hypertension, suggesting the possibility that their blood pressure readings tend to be high because they often feel ill at ease in a health care facility. I then go on to make some general remarks about interaction across ethnic and class lines. I conclude with some remarks about morally correct behavior in an asymmetrical power relationship.

Two final introductory points. First, health care practitioners include both nurses and physicians. In fact, in some cases, nurses may play a more vital role than do physicians. I shall often remind the reader of the role of both by referring to both nurses and physicians throughout this essay. Second, there are cases where the power differential between the patient and the health practitioner is diffused by the social standing of the patient. If the patient is Mother Teresa, a head of state, or some other figure of immense social standing, the power of the physician is diffused by the social standing of the patient. The arguments of this essay do not apply to instances of this sort.

Situating Trust

Characteristically, trust is a matter of voluntarily making oneself vulnerable to another person, who is both aware and accepting of this, with the belief that the person in question will not harm one, even though such harm could be done with impunity (1). Trust can be explicit or implicit. If I permit my child to visit your house in order to play with your child, I will have explicitly entrusted my child's care to your hands, which means a number of things implicitly. I will have implicitly trusted you not to poison her, to call me if she suddenly gets ill, to treat her fairly,

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and so on. I will most certainly not tell you not to poison her; indeed, it would surely be an insult if I did. Or, in any case, if I must make this request of you, then perhaps I should not be trusting my daughter to you in the first place. Or, to take another example, if I ask you to look after my mail while I am away, I am explicitly trusting you to gather my mail and put it in a safe place; I am implicitly trusting you not to read it or let someone else do so. Again, it would be odd if I were to ask you to watch after my mail, and then go on to implore you not to read it, though surely I expect you not to. Once more, if it were necessary to implore you not to read it, then that would be reason to suspect that perhaps I should not be trusting you to look after my mail in the first place.

It is difficult to imagine a case in which explicit trust does not involve implicit trust. There is nothing to be said for trusting you to save me from the lions if I know that you are going to throw me to the sharks. And so if I am explicitly trusting you to do the former, then I will be implicitly trusting you not to do the latter. Let us consider trusting you to be honest in speaking or writing on my behalf, when I have asked if you would do so and you have agreed. I am not asking you to speak the entire truth about me, for that may be considerably more than what anyone has a right to know. What is more, there are various ways of presenting the truth, not all of which are equally positive. While it may be true that I have not published much, this truth can be said in both flattering and unflattering ways. If I have trusted you to write a letter on my behalf, I will also have trusted you to present me in a positive light; doing that is more than a matter of telling the truth. In fact, it is sometimes a matter of not telling certain truths. After all, honesty is not an all or nothing virtue. That is, a person is not considered to be honest if and only if she tells everything she knows.

I have gone on about implicit trust precisely because it is difficult to imagine cases of explicit trust that do not involve implicit trust. Why is that? The answer has in large part to do with the fact that life is textured. That is, in order to perform the task with which one has been explicitly entrusted, there are, typically, an indeterminate number of other things that one has to do. Some of these things are knowable, because they hold generally. But others are not, because they are tied to the particular circumstances that come about, but whose coming about cannot possibly be predicted. That homes can catch on fire, it is knowable; when this will happen is not knowable, and so the possibility is something that a person would typically take into account in asking someone to babysit for him.

There is more to be said about trust. We can bring this out by looking at what is perhaps the most dramatic expression of trust known to humanity, a trust that occurs between unequals, namely the child's trust of its parents. From the outset, parents have what amounts to complete power over the child, who is utterly dependent upon them for its well-being. There is very little that a 3- or 4-year old could do to prevent itself from being harmed by its parents, if they should desire to do so. If Freud is right, early experiences of parental power are very nearly decisive in determining how the child develops. In particular, they determine the motivational structures that the child comes to have. One of the most morally beautiful aspects of parenting occurs when parents successfully convey to their child that they will not abuse their power, that the child can trust them regardless of the extraordinary power differential between them. And surely it is right to characterize this as morally beautiful, for there is no set of laws on earth which could ensure that parents not abuse their power over their child.

Offhand, it seems natural to think that the parent-child relationship is the only social relationship involving unilateral trust. Not so, however. Systematic inequality can also be a basis for unilateral trust. What is more, wherever we have unilateral trust, considerations of implicit trust abound. This brings us to the field of medicine, to which I now turn.

Patient and Health Care Practitioner

It is a truism that the patient-health practitioner relationship is one of trust, in which the patient trusts the physician. As patients, we go to the physician to learn about ourselves, or to have complicated things done to our bodies that require considerable knowledge and skill. We are given information about things that are going on within our bodies and instructions to follow in order to ameliorate undesirable conditions. To put a finer point on the matter, physicians make authoritative utterances about the patient's body and may perform various procedures on it. They make this or that diagnosis and assert that this or that course of action is necessary to remedy or arrest the illness. To be sure, a patient may thank or compliment a health practitioner. But such actions or words are not tantamount to the patient making authoritative utterances about the health practitioner's body.

Nor, in general, is the patient in a position to make authoritative utterances about any other aspect of the practitioner's life.

Interestingly, our trusting a physician is not just a matter of whether his or her expertise is adequate. To be sure, we want this to be the case. But there is also something else that is absolutely necessary, namely feeling at ease with the physician. This embodies a cluster of notions. Among these are feeling comfortable with what the physician is doing and saying. This, in turn, is tied to the belief that one is being taken seriously by the nurse or physician.

Is the nurse or physician actually listening to what we say, to the nuances that we give to the description of our bodily pain and predicament? Does what we say matter to her or him? Or is the health care practitioner merely waiting for us to finish speaking in order to be able to get on with our physical assessment. Being taken seriously by a physician is of great importance, for obvious reasons. No matter how much knowledge the physician has, nothing whatsoever alters the fact that it is our bodies to which the physician is attending. Accordingly, how we feel about what is to be done to us matters, even if we are mistaken. A hostile, close-minded house painter is one thing; our walls have neither feelings nor preferences nor fears. As humans, we have all three, and a nurse who ignores them cannot possibly gain our confidence, no matter how great his or her expertise. It is not possible for the nurse to ignore us in this regard and, at the very same time, take us seriously. This is because no amount of expertise can render irrelevant our subjective perspective (2). Contrary to what the health practitioner says is supposed to happen, something may cause us pain and we do not want the practitioner to ignore our very real pain on the basis of professional expertise about what is supposed to happen.

Taking another person seriously is very much a human phenomenon. It involves the presumption that a person has self-knowledge or, in any case, that where the person is mistaken about herself this may in fact be instructive. Inappropriate fears often reveal mistaken assumptions about things, especially in a context where a person is relatively underinformed. To some patients, 14 grams may sound like an awful lot, whereas one-half of an ounce does not. If we take a person seriously, we suppose that what he or she says has significance even if we do not fully grasp that significance. Our failure to grasp a remark should leave us wondering what the person really intended to say. If we take a person seriously, we are less likely to challenge the plausibility of the person's statement than to try to fathom its meaning. By contrast, we do not take the drunk on the street seriously. One sure indication of this is that we spend no time whatsoever trying to make sense of the remarks he hurls at us.

Significantly, whether or not we are taking a person seriously is revealed almost entirely by our non-verbal behavior. To be sure, I can tell someone that I am paying attention to what she is saying. But whether she will actually be convinced by that utterance will depend on her assessment of my non-verbal behavior.

Human beings are better monitors of human behavior than we tend to realize. Two examples suffice to show this. Consider flirting, something which can take place in a matter of seconds. Yet human beings are remarkably accurate with respect to whether a person is flirting with them as opposed to just staring at them or looking past them. If flirting took hours, human beings would be very different creatures, indeed. The second example comes from the parent-child relationship. In a loving parent-child relationship, a child is utterly convinced that its parents love it long before the child can fully understand the words "I love you." From the standpoint of child development, if this conviction came only in the wake of the child's having mastered the language well enough to understand fully the words "I love you," then either human beings would be different creatures or it would already be too late.

In short, while a physician may tell us that he or she is taking us seriously, we are not likely to believe this if the physician fails to exhibit the appropriate behavior in his or her interactions with us.

Drawing upon J.L. Austin's classic work (3), another way of putting the point just made is that taking another person seriously is not a "performative utterance" in the way that promising is. When I say to you "I promise," I have thereby done so, in the absence of certain factors that defeat this (for example, I was ordered at gunpoint to say those words). When I utter "I promise," I may not even be sincere, in the sense that I may hope with all my heart that you insist that I not keep my promise, whereby I get the benefit of having promised without having to carry it through. An even better example in this regard is the utterance "Congratulations!" In so uttering, I thereby congratulate you, even if I deeply resent the fact that you won.

It is true that an actor could come across as taking another person seriously when in fact he is not doing so. And people can feign concern, even going so far as to cry. It is instructive, however, that people who are capable of crying in the absence of genuine concern are said to be shedding crocodile tears. But feigning concern is exceedingly difficult to do at will without some foreknowledge that one will need to put on a show of concern. And that we have the name "crocodile tears" suggests that even so salient a show of concern as shedding tears may not be convincing if it is not done in just the right way. There is little reason to believe that the typical physician could systematically feign taking a person seriously.

A nurse or physician who has subtle contempt for this or that ethnic group, or for persons of a lower social class may fail to take a patient seriously if the patient comes from one of these social categories (4). And, most unfortunately, the health practitioner is apt to be greatly self-deceived in thinking that he or she has successfully concealed this contempt. In this context, it may be worth mentioning that people can be quite self-deceived about the extent to which their lives actually measure up to the high ideals of equality that they embrace. Specifically, people often make the fallacious assumption that their general sense of good will towards others—different ethnic groups, in particular—precludes their having any biases towards others. But this is not so. Good will is compatible with a multitude of moral failings. For example, good will is quite compatible with an absence of understanding, and an absence of understanding is very fertile ground for stereotypes and biases. Again, not understanding others is very fertile ground for having an irrational fear of them, fear being one of the seeds of hostility.

Good will is not enough. It is not enough to prevent the operation of biases and misconceptions. It is not enough to preclude feelings of contempt and disdain. It is not, in and of itself, a barrier to being misguided in one's thinking about people of other ethnic groups.

Being Seen as an Other

I would like to begin this section with a particular case. The claim is that the percentage of blacks who suffer from hypertension is significantly higher than for people in other groups. No one quite knows why. There has been talk about the kind of foods people eat. Decades ago, this consideration might have seemed plausible enough, but not nowadays. Chips, dips, and fast-food, all of which help contribute to hypertension, have become an American lifestyle. Certainly, nowadays, neither blacks nor any other group has a monopoly on poor eating habits. Yet hypertension remains more prevalent for blacks than for those in other groups. In what follows, I offer a speculative explanation in line with my reasoning thus far.

Here is a general principle: In any context where we feel at a disadvantage, we feel ill at ease. A quite neutral illustration of this would be an adult trying to speak the foreign language of the country that he is visiting.

In a language that we speak fluently, people may say the most unexpected things when we approach them with a question. While we may be stunned or puzzled by the response or even at a loss for words, we at least know that the response is utterly irrelevant. But when we barely know the spoken language, we are thrown by the smallest departure from the script that we have prepared. For example, we ask for french fries at a McDonald's in Paris. Indeed, we do this with flair, putting "S'il vous plaît" (please) at the end of our request. But the counter person comes back with "Sur place ou emporter?" and we suddenly have no clue as to what the appropriate response should be, discovering along the way that neither "oui" or "non" works, since what we have been asked is whether we want to eat the food there or take it with us. We had not anticipated that particular question and do not know what it means.

Unless one has the self-consciousness of a fly, it is impossible to feel completely at ease in social contexts in a country where one does not speak the language, as the most routine conversations are anything but that. Good will, of course, is of the utmost importance. Still, it is no substitute for a vocabulary, the absence of which makes one feel somewhat ill at ease. Why? Because one cannot participate in even the most routine conversation without running the risk of making a blunder; what is more, one cannot easily recover from a blunder once made. This example shows that even with good will very much in place, there are social contexts in which we can feel ill at ease if there is merely an impediment to our being a participant in a conversation. We need not have been wronged or feel threatened. Nor need we be of inferior social status. All the same, I would imagine that if one were to take our blood pressure in social contexts where we do not speak the language, it would be somewhat higher than normal, simply because we feel somewhat ill at ease. In a word, then, active ill will is not necessary to render a person ill at ease.

I have suggested that there is a correlation between hypertension and feeling ill at ease, pointing out that it is possible to feel ill at ease even in contexts of good will. In view of the discussion in the preceding sections, the relevance of this suggestion to the issue of hypertension among blacks is perhaps obvious.

To begin with, it is generally agreed that stress contributes to hypertension. Second, an environment in which individuals feel ill at ease is conducive to stress in those individuals. Next, individuals are most certainly likely to be ill at ease, and so to experience stress, when they are not being taken seriously by someone who is making authoritative assessments and judgments that they may not fully understand, concerning their health and bodies, and that individual has a certain degree of power over them and their bodies. Finally, notwithstanding enormous goodwill, it is possible for physicians and nurses who embrace ideals of equality to have untoward feelings towards blacks, as a result of which they (the health practitioners) fail to take blacks seriously. So, health centers may very well be a variable in blacks' displaying high blood pressure.

Two caveats are now in order. The first one is that, of course, I most certainly have not meant to suggest that there are not any physiological factors which are relevant to hypertension being prevalent among blacks. There are undoubtedly a multitude of factors that contribute to hypertension. But if indeed stress is one of them, then the consideration that I have advanced (of feeling ill at ease with the physician) must certainly be taken into account.

Secondly, while I have used the case of blacks as a specific illustration of the way in which feeling ill at ease with a nurse or physician may be a factor in persons showing signs of hypertension, it should be obvious that the argument can be extended to other groups and to persons from a lower economic class. Nor does my argument presuppose that only whites can make persons feel ill at ease. That is preposterous. A black health practitioner could render an Asian patient ill at ease. Or conversely, where the health practitioner is Asian and the patient is black. An Indian nurse or physician could render a Latino patient ill at ease. Or conversely. And so on. What is more, even if the physician and the patient are of the same ethnic background, it is possible for the physician to render the patient ill at ease; for members of the same group, as defined by some external feature, can have misunderstandings of other members of that group where there is a division along class or cultural lines. The categories of black and Asian, for instance, include a multitude of peoples. It is surely not a given that all blacks or all Asians understand one another, as there have been histories of strife between different black groups and different Asian groups.

Now, I should point out that sometimes it is not in any way the health practitioner's fault that a patient feels ill at ease with the practitioner. Sexist attitudes among patients, regarding who might properly serve as their physician come readily to mind here. But the same holds equally well for racist attitudes regarding who might properly serve as a physician. That there are men who hold that a woman cannot be a first-rate physician, and whites who hold the same regarding blacks, hardly needs pointing out. The patient, too, may bring biases to the office of a health practitioner. That having been said, however, we must not lose sight of the fact that (as I remarked earlier) the physician-patient relationship is an asymmetrical power relationship that mightily favors the physician, because it is the physician who makes the authoritative utterances about one of the most personal aspects of a person's life—namely, the person's body.

Conclusion: Moral Goodness Beyond Rights

Rights talk is all the rage nowadays. Nauseatingly, there are rights and counter-rights to just about every imaginable activity. In some cases, it is far from clear what it even means to have the right in question. What could it mean to have a right to be stupid or wrong, as some have claimed? But one thing that is clear is that the focus on rights skews the moral landscape. Does anyone have a right to be greeted with "Good morning"? Surely not! Yet a world in which people did not so greet one another in their social interactions would be a much less desirable place in which to live. The language of rights does not always make for a morally richer world.

Do patients have a right to a physician who understands their background and experiences? Does a physician have a moral duty to learn these things about his or her patients? In general, does a physician have a moral duty to put her or his patients at ease? Whatever the answer to these questions might be, a physician does an immeasurable moral good in learning about her or his patients, and doing as much as possible to put them at ease. Being at ease with another is an intangible moral good of enormous significance, to which the language of rights cannot begin to do justice. In fact, even if there could be such a thing as a right to be put at ease, it would hardly be a right that one would want to claim against others. For only purity of heart and depth of conviction could make it possible for one person to succeed in putting another at ease. But these are traits of character, and traits of character cannot be legislated.

If nurses and physicians are to succeed in making the patient feel at ease, this has to be done because they want to do so. But if good will is not enough, then it follows that, in order to put the patient at ease, physicians must cultivate a concern for others that extends beyond good will— a concern which, though it cannot be demanded as a right, constitutes a recognition of the humanity of the other. For we are not just formless human beings. Each of us is a human being with particular qualities and needs. And while it may be a contingent feature of life that we came to have one set of particular characteristics rather than another, these particulars nonetheless become a constitutive feature of the life that we live. Thus, to be indifferent to these particulars is to be indifferent to a person's humanity as it has taken expression in his or her life. And this no morally decent person should want to do.

I believe that each of us has the moral resources to inspire trust and put others at ease, if only we would find doing so desirable, if only we should so choose. For this is a choice that we must make; it will not just happen. It is possible to be harmful in our interactions with others without having active ill will. So if health practitioners choose not to be informed about the particulars of a person or a group of persons with whom they interact regularly, if they steadfastly insist, evidence to the contrary notwithstanding, that good will suffices for the tasks at hand, then it may be legitimately asked whether their resolute unwillingness to alter their behavior is itself a species of ill will. In the name of just doing their job with good will, every health practitioner—every nurse, every physician and every social worker in the health professions—would do well to bear this consideration in mind. After all, trust is a moral virtue in its own right, a moral virtue that is not reducible to good will.

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Diagnosing Death:

What's Trust Got to Do with It?

Lance K. Stell, Ph.D.

Abstract

Physicians licensed to practice medicine have enjoyed socially endorsed, legally underwritten status-trust to a remarkable degree. However, such trust is not endorsed equally by all segments of American society, most notably, by African Americans. Because physicians underappreciate this fact, they fail to understand how routine medical behavior can disproportionately exacerbate African Americans' pre-existing suspicions. On the other hand, overinterpretation of this fact needlessly risks despair. A theory of trust provides guidance in resolving clinical conflicts. **Key Words:** Brain death, diagnosing death, minorities, trust, organ donation.

WHAT HAS TRUST got to do with diagnosing death?

Quite a lot! Especially in a setting where: death is unexpected; its cause is a neurological catastrophe, the worst damage from which is largely unapparent; the full range of ICU resources have been deployed to support the patient's respiration and blood pressure, to maintain appropriate fluid volume and electrolyte balance; neurological criteria have been used to diagnose death; the family interprets "routine request" (albeit, ineptly made) for organ donation as evidencing insufficient regard for the patient; unit personnel use clinical language which the family takes as sending a "mixed message" about the fact of death; the physician(s) are unchosen strangers; and the deceased's family is African American, whose perceptions of the health care system deprive "Trust me, I'm a doctor" of reassurance or persuasion.

Case

Early on a Friday evening, a formerly healthy African American male in his early fifties is found unconscious in his apartment by a friend. The patient is unarousable and seems not to be breathing. Resuscitative measures are administered successfully in the field. The patient is admitted to the neurosurgical intensive care unit and is placed on mechanical ventilation. The on-call neurosurgeon's initial exam yields a preliminary diagnosis of a major cerebrovascular accident. A CT scan of the patient's head confirms the diagnosis, revealing a massive intracranial hemorrhage involving virtually the entire left hemisphere, a probably unsurvivable injury. Initial attempts to contact next-of-kin (who live out of town) prove unsuccessful. The neurosurgeon orders maximum supportive measures over the weekend, pending a comprehensive review by the unit attending on Monday morning.

By Monday morning, the patient's neurological status has deteriorated markedly. He is now totally unresponsive, pupils fixed in mid-position, blood pressure unstable. The attending neurosurgeon increases pressor support, verifies that the patient is not hypothermic and that his blood gases are within appropriate ranges, and then performs an "apnea test." The patient is observed for

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10 minutes and displays no respiratory drive. The attending documents probable "brain death." In mid-afternoon, the attending repeats the protocol with the same results. He documents the diagnosis of "brain death" and orders the patient to be removed from "life-support" and to be transported to the morgue when asystole occurs. It is six in the evening. The attending is about to leave the hospital for the day. He asks the unit charge-nurse to attempt to contact the patient's family again. This time, she succeeds in contacting a family friend and leaves word that a family representative should call the hospital as soon as possible.

Just as the attending is about to leave the unit, the patient's mother calls. The neurosurgeon takes the phone, summarizes how the patient was found, reiterates the clinical course, and concludes by telling her that her son is "brain-dead." He tells her that "life-support" was in the process of being withdrawn.

The patient's mother reacts emotionally. She says it is impossible for this to be true. He was "just fine" when she had seen him on Friday morning. She says that surely there has been some mistake. She implores the physician not to do anything until she gets there. The neurosurgeon agrees reluctantly to delay implementation of his orders. He concludes the conversation by mentioning to the mother that representatives from Life-Share may want to meet with her in light of the decision to delay removal of "life-support." He adds that whether this conversation occurs or not, is entirely up to her, and she doesn't have to talk to a Life-Share representative.

Even though the family lives 30 miles away, within an hour the patient's mother and 10 family members (including several from New Jersey and New York who had just arrived to visit the patient's mother) have assembled in the unit. The mother approaches her son and comments that he is warm, looks like he's sleeping, and adds, skeptically, that he "looks too good to be dead." Another family member notices that the monitor is not "flat line" but instead displays values for heart rate and blood-pressure.

The family members huddle briefly and then, through the patient's older brother, announce that they do not accept what the physician has told them, that they want a second opinion, and that they intend to make all medical decisions on the patient's behalf, specifically any decision to withdraw "life-support." Another family member comments that the doctors seem more interested in getting the patient's organs than in taking care of him. To family members, it seems apparent that the equipment which the doctor himself calls "life support" is working. It "supports" the patient's vital signs, as they can see for themselves on the monitor. The family regards the doctor's order to withdraw support as revealing a plan to let the patient die to get his organs.

The physician is emphatic that he has not made a mistake. The patient is "brain dead." The "signs of life" the family notices are present only because of the drugs and the machines. He repeats his intention to withdraw "life-support" immediately. He claims a legal responsibility to determine whether death has occurred and to pronounce it. Once he has done so, he maintains, it is unethical to treat the dead as if they were alive. He insists there is no conspiracy to get the patient's organs. On the contrary, the law requires that he explore family willingness to donate. The family circles around the bed and refuses to move aside. The physician asks the charge-nurse to call hospital security.

"Trust Me, I'm a Doctor": A Theory of Status-Trust

Continuously monitoring others, out of fear of the harm they may do, is burdensome (1). Trusting them not to cause harm lightens the burden, but presents a risk—trusting the untrustworthy. The risk increases in cases where one relies on another to act on one's behalf, to use his expertise to carry out one's will or to promote/protect one's interests. The grant of liberty necessary for effective agency creates an opportunity for the agent to betray trust for personal advantage (2–4).

The reliance problem compounds when the agent serves in multiple capacities simultaneously, e.g., not only as one's physician, but as physician-advocate for other patients, as a public health officer, as deputy law-enforcement officer, duty-bound to report to authorities certain suspected violations, as required-requester for organ donation, as resource economizer, etc. Awareness of multiple agency creates reasonable fear about how one's physician ranks conflicting obligations (5). The reliance problem further compounds in relations with minorities who suspect the trustworthiness of institutional officials generally, and surmise that white-coated strangers tend to rank lowest the obligations owed to members of their minority group (5). The resulting mix of anxiety and suspicion readily transforms routine clinical behavior into confirmatory evidence for worst fears, especially when the agent is an unchosen stranger. Choosing the agent mitigates fear to a degree. We tend to trust more the agents we have chosen or with whom we otherwise identify, whatever the wisdom of such choices.

Trustworthiness is like credit-worthiness. Each implies desert. But desert cannot be determined directly, so everyone must use surrogate measures instead. Selection of surrogate measures involves a trade-off between accuracy and ease of use. Rough and ready measures (e.g., those based on socially endorsed stereotypes) promise ease of use, but guarantee comparatively inaccurate estimates of a person's ability and determination to repay debt or fulfill professional obligation. More finely crafted surrogate measures promise greater accuracy but are harder to master, require gathering harder-to-get information, and take longer to apply. However accurate or mistake-prone, surrogate measures only provide indirect estimates of one's underlying credit-worthiness or trustworthiness.

In general, therefore, the amount of trust anyone actually enjoys depends on the perceptions and estimations of others, rather than on one's genuine "desert." In addition, one's confidence that one deserves trust can influence (not always favorably) the amount of trust others will accord. The display which conveys self-assurance to some, intimates arrogance to others. And finally, positive or negative perceptions by others of one's profession and professional colleagues are also a major factor in the amount of trust one will receive.

Historically, the medical profession in the U.S. has enjoyed legally underwritten, socially endorsed "status-trust" to a remarkable degree (2, 4). Unlike other licensed professionals (e.g., lawyers, engineers), who have been subordinated to fiduciary law to regulate foreseeable conflicts of interest with those they serve, the medical profession is trusted to regulate itself (4, 6).

The medical profession exercises near-absolute control over the number of medical schools that exist in the U.S., as well as their admissions criteria and curricula. Licensed physicians establish, review and occasionally discipline graduate medical education programs and residencies. Licensed physicians dominate state medical licensing boards. They have near-exclusive control over professional peer review, over continuing education requirements, and over member discipline. They are trusted to determine legally when a person dies. They do so using tests they devise and validate. They evaluate, determine and certify disability for insurance purposes. The prescription system secures to them exclusive authority over access to many drugs and medical devices, enabling manufacturers to charge higher prices than would otherwise be possible.

Such extraordinary professional autonomy cannot be explained by reference to expertise alone (2). Individuals who have acquired medical knowledge, even to a high degree, have no right to practice medicine, no right to social privilege or to enhanced economic opportunity (7). Yet a licensed physician does. By law, he obtains his privileges from other licensed physicians charged with the responsibility to evaluate his skills and character on society's behalf. By and large, only other licensed physicians can restrict or abolish the right to practice. All this serves to reinforce a perception that a licensed physician owes his professional life to other licensed physicians.

How might the medical profession's extraordinary, legally created autonomy be justified? Perhaps like this. In theory, the license to practice medicine signifies that its holder is party to an "understanding" between the medical profession and society (2). In exchange for a legally protected monopoly over defined services which the license to practice gives them, medical professionals as a group incur obligations to promote the public's health care interests, to define and uphold standards of care, to pursue excellence, to exercise stringent peer review, and to abide by an altruistic ethic of service. This service-ethic imposes on the practitioner duties to advocate vigorously for his or her patients' health interests, to use learning, skill and judgment for the individual patient's benefit, and to resolve conflicts of interest in the patient's favor.

The "understanding" between society and the medical profession establishes, gives content to and (supposedly) justifies the public's trust in it (2, 8). The public's trust in the medical profession has two aspects, one cognitive, involving widely shared beliefs about the profession's knowledge, skill and character, the other motivational (9), involving dispositions to take seriously what the profession as a whole thinks about health and illness, to think well of, to speak well of and to rely on licensed physicians more or less exclusively for health care. These cognitive and motivational elements constitute the medical profession's status-trust with the public.

How much status-trust the medical profession enjoys varies with time, between social and ethnic groups, and between individuals. Anything that influences social perceptions of doctors—breakthroughs in medical science, Medicare fraud, dramatic television shows, exposés on *60 Minutes*—can affect the profession's status-trust, determining how much or how little it devolves to individual practitioners. In short, status-trust helps determine the degree of trust which a randomly selected patient tends to place in a randomly chosen, licensed physician.

Status-trust contrasts with "merit-trust." Merit-trust, which has analogous cognitive and motivational elements, is based on perceptions of an individual practitioner's trustworthiness. These perceptions are to some degree independent of those grounded in professional status. Such perceptions may be accurate or fanciful. They may derive from mismeasures, e.g., the physician's apparent empathy, rather than his or her dutiful pursuit of a rigorous continuing education program. Merit-trust in one's own physician is commonly associated with affection and loyalty. It may be shallowly based, because of mere familiarity or because of the fact that one has chosen her, or it may be based more deeply, because of significant health crises she has skillfully seen one through.

Status-trust benefits physicians generally, by motivating patients to accept inconveniences they would not tolerate otherwise—long waits for service, very brief face-to-face visits, health care information poorly explained, etc. Indeed, status-trust motivates patients not only to tolerate, but even to defend objectionable conduct widely characteristic of the profession. For example, physicians' chronic lateness or preoccupation tends to be rationalized by invoking unforeseeable but presumed weighty responsibilities, rather than criticized as evidence of poor time management (9). It motivates interpreting the professions' restrictions on physician supply as evidence of its high standards, rather than as shrewd income protection. Status-trust motivates patients to accept medical pronouncements which deny appearances or seem contrary to common sense, e.g., that someone who looks well has cancer and is dying, that it is necessary to continue taking medicine even after one feels better. Status-trust enables physicians to substitute assertions and commands for lengthy accounts and explanations.

Status-trust in the medical profession is valuable to society. It economizes on "knowledge costs" for the layperson. Rather than *caveat emptor,* which recommends arms-length caution when dealing with non-licensed professionals, legally underwritten status-trust permits patients to assume that it is not risky to disrobe at the request of a white-coated stranger (8). Status-trust entitles patients to believe that they will be examined, not fondled, and that information disclosed in the clinical encounter will be kept in confidence.

Status-trust has enforceable content for patients. It vests in them a legal right to expect that any licensed physician possesses the degree of learning and skill ordinarily possessed by his professional peers who do similar work, that he will use his best judgment and exercise reasonable care in the exercise of his skill for the patient's benefit. In short, status-trust entitles patients to believe that the holder of a medical license will perform within "the professional standard of care." Should the physician harmfully betray status-trust, he is liable in damages for malpractice (6, 10).

The medical profession's obligation to promote the public's health care interests (part of the "understanding" referred to earlier) is vague, but not totally lacking in content. Equality of opportunity and fair competition are important social values in the United States. Our society ought not to create privilege-to-practice monopolies unless the health care interests of all citizens are promoted equally as a result. Just as public service monopolies are granted with the understanding that service must be provided to all citizens within a geographical area, so, it might be argued, medical monopolies must do the same. The medical profession's acceptance of its legally protected monopoly implies a duty to take equal citizenship seriously. Arguably, the idea of respect for equal citizenship imposes on the medical profession ethical duties to make its services equally available and to require members to practice medicine without discrimination.

My sketch of the rationale for medical autonomy based on social "understanding" should not be taken as proof that state-licensing of medical professionals is a good idea, all things considered. Much can be, and has been, said against it. It has been argued that the profession's most powerful voice has repeatedly frustrated attempts to implement any aspect of the "understanding" which threatens physicians' incomes, that it has refused to demand pro bono service to the poor as a professional responsibility, that licensed physicians behave more like a fraternity than a profession when it comes to weeding out incompetent or unethical practitioners, that continuing medical education is a euphemism for tax-deductible vacations in pleasant places (2–4). All of these claimed defaults are predictable from the premises of an economic theory of politics (rent-seeking theory) (11).

"I'm a Doctor (Don't Trust Me)": Status-Distrust

The contrary of status-trust is status-distrust. It too has cognitive and motivational elements.

Status-distrust is not merely the absence of status-trust. On the contrary, status-distrust involves skepticism that the medical profession takes seriously the responsibilities which derive from its "understanding" with society, for example, the responsibility to treat all citizens equally and without discrimination (5).

Status-distrust of the medical profession may manifest in many ways. It might combine skepticism regarding the profession's altruism with a selective focus on aspects of the American Medical Association's lobbying efforts which seem self-serving, rather than on those which might seem more public-spirited. It may include the tendency to pay more attention to stories about physicians' errors and ethical lapses than to those about their sacrifices and successes. And it may generalize these shortcomings to all or most members of the profession.

Status-distrust motivates one to expect bad treatment from white-coated strangers, to challenge or disobey them rather than to be compliant. Motivated skepticism of doctors explains how routine clinical inconveniences such as misplaced charts, short visits, failures to listen attentively, and physician assertiveness would tend to be interpreted as disrespectful, contemptuous, or evidence of bad faith.

Status-distrust of physicians is more widespread among African Americans than among whites (12 – 14). Studies show that African Americans are twice as likely as whites to rate their health care services as fair or poor. Indeed, one study showed that 8 of 10 African Americans perceive U.S. society as unfair, especially with regard to its economic and legal institutions. Another recent study found that 57% of African Americans vs. 31% of whites think that the U.S. economic and political system is unfair (5).

These findings have obvious relevance for efforts to improve the treatment African Americans receive socially and politically, including improvement in the quality of health care services delivered. But their implications are even more striking in the context of the theory of status-distrust. That African Americans disproportionally regard social institutions as unfair implies that they will tend not to identify with those institutions, not feel a sense of "ownership" of them, not regard their operations as "valid" (on the assumption that one tends not to identify with what one regards as bad or unfair). Tending not to identify with an institution because one believes it is unfair will motivate one to place reduced status-trust in its officers.

African Americans' disproportional status-distrust of the medical profession will tend to have negative consequences for physician-patient relations even when there is no "objective" disparity in service. Since African Americans' motivated skepticism regarding physicians is comparatively strong, doctors simply do not have as much trust to "bank on" with this minority as they do with others (13, 14). This means that merit-trust must be won on an individual basis, to compensate for the marked deficits the profession as a whole has in the eyes of African Americans. Physicians who are African American may enjoy a marginal gain in status-trust with African American patients based on ethnic identification, but the magnitude of the gain varies, may be obliterated at the first utterance, and not infrequently is swamped by status-distrust of white-coated strangers.

The Trust-Inventory: Building Merit-Trust

The likelihood of a successful clinical encounter is reduced when a physician attempts to bank on trust he does not have. If the patient or other decision maker distrusts the profession as a whole, not to mention all powerful institutions, and if the clinician himself has built up little or no merit-trust with the individuals involved, he will not enjoy the luxury extended by the happy assumptions that doctors are not only highly skilled, but mean well and should be believed (and obeyed). If so, determining how much trust one has to work with and how much one may need in the circumstances is the first step in forestalling disaster.

What might such an inventory have taught the physicians involved in the case presented earlier? Status-trust = low. Merit-trust = zero. Amount of trust needed? More! In addition to the disproportionally high status-distrust of physicians among African Americans, and the fact that the physicians in this case were not chosen by the patient or family, there were several compounding factors. Studies in the medical literature reveal that many citizens doubt the validity of "brain death" (15, 16). One state (New Jersey) recognizes a right of families to veto the use of neurological criteria to determine death. Another (New York) urges physicians to "accommodate" family concerns about the validity of brain death (17). Recall that some of the family members involved in this case were residents of New Jersey, a fact neither appreciated nor explored.

Fear of incorrect diagnoses of death has a long social history (18). News accounts of recent medical errors in diagnosing death have lodged firmly in the popular mind. High status-distrust will tend to highlight such accounts. Robin Cook's *Chromosome 6* and the film *Coma* exacerbate public fear of organ transplantation and the motives of medical professionals who do it. African Americans' suspicions of organ transplantation are well-documented, even in living-related donor circumstances (12).

Also, the physicians in this case were asking family members to deny the validity of what their senses seemed to tell them about the patient's condition (he didn't have a mark on him, he looked too good to be dead, he felt warm to the touch, his monitor displayed "vital signs"). The clinical language used with the family, although not at all unusual in an intensive care unit, exacerbated suspicion (19). "Brain dead" when conjoined with "life-support" invited the family to think that the patient was not really dead, and that removing "life-support" would kill him for sure.

What trust-building efforts actually helped in this case? All displays of authority were halted. Hospital security forces were asked to leave the unit and told not to return. Representatives from Life-Share were asked not to approach this family for organ donation. The family was asked to ratify this request, which it did.

The family was invited to a conference room, with an assurance that no equipment would be removed from the patient in their absence. Only one representative from the ethics committee accompanied them. Despite having been briefed beforehand by the attending physician and unit nurses, the ethics consultant asked the family to educate him about what happened. Listening carefully to the family's account took 45 minutes, during which the ethics consultant said virtually nothing, neither by way of explanation nor defense. An interesting fact emerged. The patient's fiancée was suspicious that the "friend" who found the patient unconscious might have tricked or otherwise induced the patient to ingest cocaine. (All family members present said that the patient had been "clean" for three years.) The fiancée, supported by other family members, suspected that foul play had caused the patient's sudden illness. They worried that if the patient was removed from "life-support" the suspected criminal role played by the "friend" would be clouded. They were unanimous that, if the patient died, an autopsy should be performed and the police notified.

When the family seemed satisfied that their account and concerns had been fully laid out, the ethics consultant asked whether family members would permit him to invite two physicians to discuss the case—a radiologist who would review with them the CT scans of the patient's brain and a neurologist who would explain how it was possible to diagnose death using neurological criteria. The family agreed.

The radiologist showed the family a CT scan of a normal brain. He oriented them regarding right/left and explained how the films showed brain structures. Then he showed the patient's CT scans. The visual evidence of the patient's stroke made a notable impression. Family members asked many questions, especially whether cocaine could cause such damage to the brain.

The neurologist explained to the family what is involved in diagnosing death by neurological tests (17, 20). He clarified that these do not amount to a "new" definition of death, by relating these to traditional bedside findings (general unresponsiveness, pupillary non-reactivity, apnea and absence of heartbeat). He explained that all the traditional tests implicated the absence of brain functions directly or indirectly (21). General unresponsiveness, pupillary nonreactivity and apnea implicated the absence of brain functions directly. The absence of heartbeat, because of its dependence on breathing, implicated brain functions indirectly. The neurologist explained that the tests used to determine death in this case revealed unrecoverable, irreversible damage to the patient's whole brain. He assured the family of the certainty of the diagnosis—that the patient was dead and had been pronounced dead. Nevertheless, since second opinions have a customary place in medicine, he offered to help secure one if the family wished. They didn't. Displays of grief replaced incredulity.

The neurologist then invited the family to accompany him to the bedside for removal of all interventions. They accepted. The ethics consultant offered to call a representative from Pastoral Care. The family accepted this too. When all were ready, the neurologist took the family to the bedside and began removal of all equipment attached to the patient.

Suspicions flared again when the patient's body reacted to the removal of the interventions. This possibility had not been explained in advance. There were more accusations, but not so vehemently expressed this time. The neurologist's explanation seemed to be accepted. Displays of grief eventually eclipsed residual skepticism. Not a happy ending, not even the best that one could have hoped for in the circumstances, but less bad than seemed likely only an hour earlier.

Ethical Diagnostics

Medical diagnosis is hard. Many disease-states (not to mention the absence of disease) may be "consistent with" the presenting complaints and symptoms. Multiple rule-outs may be necessary before a diagnosis can be fixed. Ethical diagnosis is hard too. There are multiple ethical wrongs which present in a clinical setting: disordered values, damaged relationships, complex histories, confusing accounts, changing stories, twisted causal chains, bad luck and surprises. In ethics, as in medicine, performing a differential diagnosis with systematic "rule-outs" helps to avoid mistakes.

The ethicist disregarded the rule in this case. He quickly settled on status-distrust as a primary working diagnosis and ignored other plausible, even tempting possibilities (e.g., that unexpected death tends to trigger psychological "denial" more strongly than expected death). In place of a meticulous ethics work-up, he substituted a rule of thumb consistent with the theory of status-distrust.

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Distrust, Social Justice, and Health Care

Howard McGary, Ph.D.

Abstract

What steps, if any, should be taken to eliminate the distrust that many racial minorities feel toward the health care system in the United States? Is this distrust an issue of social justice or should it be viewed as an instance where people unreasonably fail to take advantage of existing opportunities? I argue that this distrust is an issue of social justice and that the state does have an obligation to eliminate or mitigate it, especially in the area of public health. **Key Words:** African Americans, AIDS, distrust, health care, justice, racial discrimination, medical ethics, Tuskegee Syphilis Study.

Most people in the United States consider health care, along with food and housing, to be "primary goods." According to John Rawls, one of the leading political philosophers of the 20th century, primary goods are things that every rational person is presumed to want (1). These goods have value to a rational person no matter what his or her plan of life might be. In his important books *A Theory of Justice* (2) and *Political Liberalism* (3) Rawls argues that the allocation of these goods is subject to the constraints of justice and that processing these goods has a bearing on a rational person's self-concept. The cornerstone of Rawls's account of social justice is his belief that the least-advantaged members of society, as measured by their possession of the primary goods, should be the gauge by which we judge the justness of the basic structure of society (4).

Because of his belief in this "gauge," Rawls endorses redistributing resources by taking some from those who are better off, if doing so will make the least-advantaged better off than they would be under any alternative arrangement. However, Rawls's critics from the political right contend that egalitarian/welfarist conceptions of justice violate the individual's right to liberty (5). And his critics on the left claim that his commitment to equality does not go far enough (6). They argue that the needs of many, especially the working class, will always go wanting in a capitalist mode of production.

As we can see, there are various ways of conceptualizing the demands of justice. In this paper, I will not explore the general question of what the correct account of distributive justice is. Instead, I shall ask whether the distrust that racial minorities, particularly African Americans, feel toward the health care system is indeed an issue of distributive justice.

Demands of Justice

No matter which account of distributive justice we embrace, when we say that an institution or practice is unjust we believe that this fact gives us a compelling reason for altering or abandoning that institution or practice. Since justice is considered to be the first virtue of social institutions, injustice demands action. The action demanded can, and often does, involve state intervention.

In capitalist societies like the United States, with a constitution that vests rights in individuals, great weight is given to individual liberty. Individuals are allowed to pursue their own conceptions of the good provided they respect the rights of others. In such a system, justice demands that we respect the rights of individuals. On any account of rights, rights violations provide us with a strong motive for change, a reason for feeling sympathetic toward the victims of such injustice, and a basis for claiming that the victims deserve to be compensated.

Discussions about what should be done now in response to the recently overturned system of legal racial discrimination have led to contrary conclusions. Some people argue that state-sanc-

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tioned racism is a thing of the past, that racial minorities should forget about that past and work to take full advantage of present opportunities (7). Others argue that vestiges of the system of legal discrimination still exist, and that racial minorities will not be able to develop their skills or reach their full potential until our society takes further steps to break down the barriers that have been created by a long history of racism (8). The position that one takes in this debate will bear directly on where one stands regarding minority distrust of the health care system.

For those who think we ought to put the past behind us, it is hard to imagine why minority distrust of the health care system should be seen as an issue of social justice. For those people who view things exclusively in terms of a current time-slice, our horrible racial history does not justify giving additional resources to racial minorities for the purpose of addressing their present distrust of the health care system.

On the other hand, those who think that this history is relevant to public policy believe that society must address this distrust as a matter of social justice, because distrust is a clear consequence of racist practices that were perpetrated or condoned by the state. For these people, affirmative action and compensatory education programs may also be necessary to bring about social justice.

Others believe that a just society does not have to try to compensate the descendants of members of racially oppressed groups, but that the good or just society has forward-looking reasons for taking the steps necessary to make itself more egalitarian and open to all. These people are not concerned about identifying wrongdoers and providing compensation to those who have been wronged. They focus instead on the good utilitarian reasons for providing resources to persons and groups that need them (9).

Distrust

Before I comment on the justness of this distrust, I would first like to say a few things about the nature of the distrust that certain racial minorities are said to feel toward the health care system. For the sake of brevity, I will limit my focus to African Americans. I also do so because African Americans are often cited as the group that best illustrates this skeptical attitude toward the health care establishment. This skepticism raises two questions: Is the distrust that African Americans are said to feel rationally grounded? If the distrust is in some sense irrational, does this mean that a just society is under no obligation to address it?

Let me begin with the second question. The mere fact that many African Americans distrust the health care system does not mean that the system is unfair to them. Nor does it directly follow that the system ought to be altered or abandoned. This depends upon why, in some sense, they distrust the system. If this distrust is based upon misconceptions, then one may initially think there is no need to change the system.

But this initial reaction may be mistaken. Just because a system is fair does not mean that it can readily be seen to be fair. Part of what we mean by a good health care system is that it is perceived to be good by those involved with it. This is why systems analysts are concerned to produce systems that are simple and readily accessible to the general public. The fact that a system is fair may not be good enough. It may also be necessary that the system can be readily viewed as fair by the general public.

A health care system that wishes to be responsive to the needs of the entire community may have an obligation to address even the erroneous perceptions of the system by African Americans. Even if the system is just and the distrust is not well founded, the long and troubled relationship between African Americans and various components of the health care system may make the distrust that many African Americans feel understandable if not justified. Given our history, perhaps an equitable health care system should be willing to make reasonable efforts to dispel these feelings of distrust. As Aristotle said, the equitable person is not a stickler for justice, especially when doing so does not serve the wider demands of morality (10).

But what should count as reasonable efforts in such a situation? In my view, two factors have to be considered. One important factor is how much this distrust affects the delivery of good health care to African Americans. Another important factor is the extent to which the costs associated with eliminating this unfounded distrust would divert funds from medical needs that may be more pressing. An equitable health care system must be willing to address these factors in a candid and public way. Doing so would make it clear to all involved that the system is concerned about the interests of the whole community, and that it is sensitive to the historical context that gave rise to this distrust.

The Duty to Eradicate Distrust

From a moral point of view, why should a just society cater to the false perceptions of a large segment of the African American population?

One might argue that an action that is not in itself immoral can be described as morally faulty if it closely resembles an immoral act (11). Immanuel Kant's argument against the mistreatment of animals is often cited as an instance of this. Kant claims that we have duties not to be cruel to animals because this type of cruelty will undermine the genuine duties that we have to persons (12). Although treating animals in a cruel manner does not violate Kant's categorical imperative, such treatment damages our benevolent feelings and makes us prone to be cruel to persons. Resemblance is taken to be a morally relevant feature of our actions because it can corrupt the actor and it can also mislead others in ways that lead to their moral corruption.

Does the resemblance argument have any application to the debate over minority distrust and the delivery of health care? Perhaps it does. If efforts by public health officials intended to reduce the risks of AIDS in predominantly African American communities resemble the strategies that were used in the now-infamous Tuskegee Syphilis Study (13), then those efforts, although not in themselves morally wrong, may be faulty because of their tendency to corrupt the actors or those who witness them. In the 40-year Tuskegee Study, there were 399 black men with syphilis and 201 controls. The unwitting participants were not exposed to syphilis by the researchers, but they were not treated for it either. Even after the discovery of penicillin, the syphilitic men in the study were not informed about their condition, nor were they treated. In order to keep the participants ignorant, there was an extensive collaboration among a variety of government agencies, private institutions, and community-based organizations. If public health programs resemble, in form but not in content, the practices in the Tuskegee Study, then this might give pause to many people in poor black communities.

Sensitive public health officials have attempted to design programs to address the distrust in poor African American communities. However, strategies like hiring "grassroots" people from the community can backfire and further contribute to the distrust because such efforts often resemble what happened in the Tuskegee Study. The Tuskegee Study used culturally sensitive techniques on the grassroots level to ensure the involvement and participation of the subjects.

Even if we assume that the resemblance argument applies to acts of individuals, it would not follow that institutional behavior which resembles immoral acts has the same effects. In fact, my intuitions about institutions are not clear. Philosopher Julia Driver has argued that one basic reason for thinking that acts that resemble immoral acts are faulty is that we may be unsure about the moral status of these acts (11). Because we are unsure, we tend to play it safe and regard these actions as morally faulty. Can we justify calling public health programs in African American communities morally objectionable because they appear objectionable to members of these communities? Some would argue against such a characterization. They might contend that to do so would be unreasonable. Are they correct?

Whether they are correct depends upon how confident we are about the safety and fairness of these programs. As the probability of their being safe and fair approaches certainty, we are inclined to reject the misgivings that African Americans have about these programs. But when the evidence of safety and fairness is not convincing, African Americans' misgivings will require greater attention. What will count as reasonable will depend upon people's past experiences, the likelihood and extent of the possible harm, and the resources that are available to cope with any bad eventualities.

But Driver also argues that there are sometimes good consequentialist reasons for refraining from doing something that is not in itself wrong. She cites the case of a woman who pays for a vase that she knows she did not break to forestall any of the negative consequences that might result from a misunderstanding concerning the broken vase (11). Similarly, a public health care system may expend funds to forestall unjustified misgivings that may result from misunderstandings about legitimate efforts to reduce the risk of AIDS and other communicable diseases. Even though there may be some negative consequences connected with pandering to people's false perceptions, the good consequences are thought to outweigh them.

There may be a more compelling argument for using state resources to mitigate the bad consequences created by an understandable, but unreasonable distrust of the health care system. John Rawls has argued that stability is an important component of a just society. According to Rawls (14),

> [t]he problem of stability is not that of bringing others who reject a conception to share it, or to act in accordance with it, by workable sanctions, if necessary, as if the task were to find ways to impose the conception once we are convinced it is sound. Rather, justice as fairness is not reasonable in the first place unless in a suitable way it can win its support by addressing each citizen's reason, as explained within its own framework.

In other words, Rawls recognizes that in order for a society to be just, citizens and public officials must comply with the rules laid down by the basic institutions of society. This compliance must be sustained over a period of time, and those who are expected to comply must feel that they have a reasonable basis for doing so. For Rawls, it would not be permissible to coerce, pressure, or trick citizens into this compliance. Stability must be achieved by addressing each citizen with persuasive reasons.

A society in which a significant number of persons believe that they are being treated unjustly will be unstable. Society, therefore, has an obligation to demonstrate that it is indeed just in order to achieve reasonable citizens' cooperation with its rules and procedures.

Many African Americans believe the health care system in the United States is not designed in accordance with principles that are publicly recognized as fair and just. If stability is important, and I think that it is, then a just society should be willing to expend resources to demonstrate the justness of the system. This is especially important where there has been a history of isolating a segment of society by race and then treating this segment in unfair ways. Since African Americans have experienced such a history, it is only reasonable that they would be skeptical about the kind of treatment they might be accorded. Special efforts will be required to overcome that skepticism. We need not go overboard and pander to unreasonable attitudes.

It is also important to note that past denials of rights have not always flowed from malevolent motives. Sometimes, attitudes that give rise to unfair treatment of African Americans have been more thoughtless than calculated. But, while we don't want to encourage wild conspiracy theories about state-sanctioned programs of black genocide, we also don't want to be too cavalier in our attitudes about the possibility that African Americans may be the victims of injustice. We have made great strides in race relations in this country, but there is still much work to be done. As a just society, we must be willing to make special efforts to ensure that African Americans can have confidence that the basic institutions of their society will respect their rights and treat them with dignity.

The Source of General Distrust

Does this mean that we should alter or abandon crucial parts of the health care system? If we are to fairly answer this question, then we need to realize that the systemic distrust that African Americans are said to feel is not limited to health care, but is part of a more general distrust of public and private institutions that have a tainted history of dealing with black people (15).

The past policies and practices of these institutions have certainly played a role in engendering this distrust. No one can seriously dispute the host of serious injustices that have been committed against African Americans by the criminal justice and health care systems, simply because they were black. But the critics would argue that these things were in the past and that *de jure* racial discrimination has been either eliminated or greatly reduced. For African Americans to continue in distrust is for them to adopt a crippling "victim's mentality." This attitude is said to prevent many African Americans from taking full advantage of existing opportunities (7) and to encourage many to blame their personal failings on racism.

Is this criticism valid? I don't think so. According to the philosopher Laurence Thomas, we must exhibit a minimal degree of trust of strangers without adequate evidence of their trustworthiness (16). But this is true only in situations that are not life threatening. When they are in danger of significant bodily or economic harm, rational people require strong evidence of the trustworthiness of the person or institution they are to rely upon. To the extent that this is true, African Americans have good reasons for skepticism about our health care system.

Does the continued existence of anti-black racism, as documented by scholars like Andrew Hacker, in his book, *Two Nations: Black and White, Separate, Hostile, Unequal* (17), undermine the belief that African Americans are treated fairly by institutions that are controlled by whites? Does this position assume that all racism must be eliminated before African Americans can drop their skeptical attitudes? Perhaps what is necessary is not the total elimination of anti-black racism, but racism that results from racist intentions. But, as our experiences with the desegregation of schools have shown us, the elimination of intentional racism is not enough (18). *De facto* racial discrimination can be just as debilitating as *de jure* discrimination. And, as we are well aware, efforts to eliminate *de facto* segregation from the schools and other walks of life have met with strong opposition. This opposition is seen by many African Americans as evidence of the lack of good will toward African Americans. If they are right, then there is a rational basis for many African Americans to be skeptical about how they will fare when they seek health care.

But even if African Americans are justified in thinking that their race could adversely affect the quality of care and attention that they will receive in the health care system, this would not show they are, in fact, being treated unjustly unless the system does not attempt to eliminate their distrust. It is not enough to make health care programs available to African American communities. Additional efforts and resources should be made available to these communities to overcome the skepticism that many members of the community have toward these programs.

The 40-year Tuskegee Study is, unambiguously, a case where people's rights were violated. It is also a case that gives even the most secure African Americans pause about what their government might do in the name of maximizing the common good. This study has planted in the minds of many African Americans the belief that the state may think it is permissible to adopt questionable means with African Americans if the ends are honorable enough. The similarity of strategies used to recruit and retain participants in the Tuskegee Study and in HIV education and risk reduction programs reinforces that belief (19).

The Tuskegee Study and the disproportionate impact that AIDS is having on the black community help to fuel conspiracy theories about black genocide. These theories in turn breed distrust in a population that is poor and resentful in the wake of persistent inequality. Given that the present political and social reality was created in large part by the unjust past actions of the state, state action to alter this reality is warranted. Whether one uses the language of rights or the vocabulary of the common good, special efforts by the state are required if public health programs are to overcome an atmosphere of distrust that took years to create. We should not be surprised to find that engendering trust cannot be achieved overnight.

Aside from the distrust of public health efforts to combat contagious diseases, we also find widespread distrust about the quality of primary health care that poor African Americans receive. Given the changes that have occurred in black communities in the wake of racial integration and the growth of a black underclass, we find fewer black professionals to serve a population with serious health care needs.

Given that trust is an important ingredient of a good doctor-patient relationship, it is especially urgent for members of the black underclass to have a trusting relationship with the people who provide them with health care (20). It is not that the doctors are generally unwilling to develop this relationship, but, given that these patients often don't see the same doctor on a consistent basis, the familiarity that is necessary to build the bonds of commitment between doctors and patients is often lacking. As the old family doctors knew, the human side of medicine may be as important as technical facility. The lack of familiarity and the consequent lack of trust, influences many poor African Americans and dissuades them from seeking health care.

This distrust and the harm that results from it cannot be addressed without making fundamental changes in the way we as a society conceptualize our obligations and priorities. And we cannot make these changes without first reaching some public consensus about how to eliminate the remaining vestiges of a system of racial discrimination. A consensus about the requirements of justice is probably the best that we can achieve in a democratic society defined by racial and cultural pluralism and a belief that each citizen is entitled to shape his or her own conception of the good life.

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Affirmative Action and the Allocation of Health Care

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Abstract

The justifications of affirmative action, the compensatory, corrective and redistributive, have been widely recognized in legal thinking. They have been applied, principally, to employment practices. They can also be applied to health care. Arguments for affirmative action in health care allocation shift the burden of proof to those who deny that racism is the root cause of differential morbidity and mortality experienced by, for example, African Americans. At the very least, these arguments mandate much needed research into the causes of minorities' poor health. Without such research, racism remains the presumptive cause of, and affirmative action the appropriate remedy for, the health care problems minorities face. **Key Words:** Affirmative action, race, allocation of health care, law and medicine, public health, medical ethics.

Affirmative action, despite its current unpopularity, is an illuminating doctrine to apply to significant contemporary data about minority encounters with the health care system in the United States, or so I will argue here. To develop this argument, I begin with a brief account of affirmative action. I then explain the principal justifications that have been offered for affirmative action. Next, I outline the typical structure of legal cases in which affirmative action was mandated as a remedy for patterns of discrimination, and show how several recent studies of the distribution of health care by race reveal an analogous structure. Finally, I note that the racial differences have not been extensively reported or discussed in the press. My conclusion is that there is a case to be made for examining whether current racially differentiated patterns in the distribution of health care reflect discrimination or reflect other factors—in other words, a case for considering affirmative action in the inspection of current health care practices.

I. Affirmative Action

The phrase "affirmative action" means: positive steps, steps in an affirmative direction, to end discrimination. The phrase made its debut in an executive order issued by President Kennedy in 1961, directing agencies in the executive branch of government to take "affirmative action" to end discrimination against blacks in their contracting practices (1). The phrase was picked up in the remedy section of Title VII, the employment discrimination title of the Civil Rights Act of 1964 (2). The exact language of Title VII is that, after a finding of discrimination, courts may order remedies such as back pay ". . . and such affirmative action as may be deemed appropriate." Affirmative action is now middle-aged: a little over 35 years old, dated from the Executive Order, a little under 35 years old, dated from the Civil Rights Act of 1964. But affirmative action has not settled into a comfortable middle age; it is perhaps more controversial today than at any time in its lifespan.

In its most general sense, "affirmative action" was a catch-all phrase inserted into the Civil Rights Act to effect a variety of positive steps intended to remedy discrimination. Many of the first steps taken under the rubric of affirmative

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action involved efforts to open opportunities to historically excluded groups. They included such actions as advertising positions widely, so that anyone interested and qualified had a reasonable opportunity to find out about them and apply for them; reevaluating announced job "qualifications," to ensure that they were genuine requirements for job performance; and establishing training and other educational programs, so that those who had not had the opportunity to become qualified for certain occupations became able to acquire the relevant skills. Each of these strategies has potential analogies for patient care. The analogy to advertising the availability of positions might be publicizing the availability of care and how to access it, so that people who might not otherwise know about such opportunities as low cost mammograms or immunizations would learn of them. The analogy to reevaluating job qualifications might be scrutinizing patient selection criteria to ensure that they are medically warranted; reevaluating the role of sex in access to clinical trials is an example of such scrutiny. The analogy to training and education might be special efforts to educate target populations about health risks or health behaviors; an example would be the efforts to educate African American men about their risks of prostate cancer and the availability of screening tests (3). Because they strive to make opportunities more widely known and accessible, such programs have been less controversial than the race-conscious selection procedures for employment and education that are under attack today. One federal appellate court, however, has very recently concluded that even opportunity-expanding programs are constitutionally problematic because they consume resources that could be spent on opportunities for all, and because they may push employers into achieving targets or quotas (4).

Affirmative action orders also mandated race-conscious selection procedures such as employment goals and even specified percentages in situations of persistent employment discrimination. Ending such race-conscious selection procedures has been the chief target of contemporary opponents of affirmative action. The controversy over goals—or quotas, in the eyes of their critics—has been heated indeed. Proponents argue that under some circumstances it is permissible to take race into account, as one factor among others, in making employment or other decisions. Some opponents claim that it is always unfair to consider race in such decisions (5). Whatever position is taken about race-conscious selection, however, it is important to remember that affirmative action refers to the whole panoply of other positive steps against discrimination, a fact which should not be forgotten in the heat of the current battle over race-conscious selection.

Many examples of the possible relevance of affirmative action to health care surely warrant discussion. The use of race in making decisions about admission to medical school was the issue in *Bakke*, the case that still stands for the proposition that diversity is a compelling interest for state systems of higher education (6). Although infrequently litigated, questions have been raised about the employment of minority physicians and other health practitioners on medical school faculties, in managed care organizations, and in other practice settings. Equity in the selection of research subjects is required by federal regulations. Proposals have been put forward by President Clinton to target funding for the improvement of minority health status. Any of these proposals warrants careful examination and discussion. My goal in this article, however, is to argue that there are lessons to be learned from affirmative action in analyzing data showing racial differences in the health care received by whites and by African Americans.

II. Justifications for Affirmative Action

"Opportunity goods," goods that affect individuals' basic chances in life, are especially important from the standpoint of justice. Without opportunity goods, people have little or a greatly reduced chance of leading a satisfying life. Otherwise quite divergent positions about justice agree on the importance of opportunity goods. To be sure, egalitarians will be concerned about the distribution of any important goods, not just opportunity goods. But those who favor equality of opportunity, or even more limited fairness in the distribution of opportunities, will see opportunity goods as central to justice. Opportunity goods give us a chance in life, make of it what we will.

Education and health care are both opportunity goods. Without education, the range of available life choices may be quite limited. Without health care, people may find themselves with impairments or illnesses that limit their life chances. Even undiagnosed hearing loss or myopia may be devastating to a child's ability to learn and thus limit the child's chances in life. Moreover, these are both goods that it may be unreasonable to expect people to provide for themselves. Both are provided through complex, interconnected systems. Health care especially—

but even education, particularly where there are special needs—involves large and not entirely predictable expenditures. And both are particularly important for the life chances of children, a population who cannot be expected to provide these goods for themselves.

In Congressional debates leading to the passage of the Civil Rights Act of 1964, concern about opportunity goods was paramount (7). The principal goals of the Act were eliminating discrimination in employment, education, and public accommodations. At the time of the Act's passage, three principal kinds of arguments were offered for the need to remedy discrimination. The first argument was the history of discrimination against blacks and the felt need to make amends for this history as well as for particular acts of discrimination. This "compensatory" argument sees affirmative action as a way of trying to make up for actual harm. It is most persuasive in the case of an identified victim and perpetrator; critics of the widespread use of compensation as an argument for affirmative action typically contend that many of the beneficiaries of affirmative action had not been harmed, and many of those affected negatively by affirmative action were not themselves responsible for any harm.

The second argument offered in the Congressional debates was the imperative to bring ongoing practices of discrimination to an end. This "corrective" argument contends that there are some practices of discrimination which can only be rooted out by imposing affirmative obligations on those who engage in the practices. If, for example, an employer makes hiring decisions on highly subjective criteria, and the data suggest that the employer selects whites more frequently than would be expected without covert discrimination, setting employment targets might be recommended as a way to force the employer to come to terms with potential inequities in the selection process. Corrective arguments for affirmative action claim that race-based criteria should be used as an antidote to race-based discrimination, not that race is a relevant factor absent the need for correction.

The third argument for affirmative action offered in the Congressional debates was redistributive: that the maldistribution of basic opportunity goods, by race, should cease. Members of Congress argued that it was unjust to allow a situation to persist in which white Americans had far better opportunities than African Americans. This argument was quite frankly "redistributive," along racial lines. Although this redistributive argument was taken seriously in 1964, it has been rejected by the current Supreme Court as a basis for affirmative action (8). Race-based redistributions of a limited good, in the view of the Supreme Court, are not narrowly tailored to further a compelling state purpose. In courts today, compensatory arguments remain viable if they are limited to identified victims; and corrective arguments will prevail on the basis of a showing of ongoing discrimination (9). It is important to emphasize that these are really very different arguments: the idea that affirmative action is needed as a corrective is rooted in the idea that there are discriminatory practices that must be ended, whereas the idea that affirmative action is important because of the maldistribution of opportunities is rooted in a more general picture of justice in society. Differential health status by race would, for example, show that there is a general maldistribution of opportunities by race, for any of a number of possible reasons, related or not to discrimination. Unexplained racial differences in the treatment patients receive might, on the other hand, raise an inference of discrimination in need of correction.

III. Affirmative Action as a Corrective

A typical corrective lawsuit would proceed according to the following pattern. The plaintiff would allege that there is ongoing discrimination in a workplace. In order to get the case started, and avoid losing on a motion for summary judgment, the plaintiff would have to bring in enough facts to warrant an inference of discrimination. This is called the plaintiff's prima facie case; it may be made out by a statistical showing of significant differences by race. Disparate hiring or promotion statistics that are otherwise unexplained would be a typical showing. Thus it would raise an inference of discrimination to show that despite similar numbers of black and white applicants meeting initial screening criteria, 70% of new hires were white.

Next, the employer may respond to this prima facie case by showing that there was a nondiscriminatory explanation for the differences. Perhaps when qualifications were looked at more carefully, the whites scored higher. Or perhaps blacks were offered the jobs in similar numbers to whites, but declined to take them. Or perhaps blacks dropped out of the pool voluntarily before offers were made, in pursuit of better opportunities elsewhere. Any of these, or many other showings, would suffice to meet the plaintiff's prima facie case with the response that there was a legitimate reason for the differences at issue.

Finally, the plaintiffs may respond by showing that the employer's reason was "merely pretextual." To make this showing, the plaintiffs must bring out evidence that the defendant's proffered reason really masked a more problematic, discriminatory reason. For example, the plaintiff might show that the supposedly better qualifications of the whites weren't borne out in fact, that the criterion relied on wasn't really related to likely job performance, or that the criterion was really only a blind for discrimination. Or, the plaintiff might show that blacks did not really drop out of the applicant pool voluntarily, but did so for problematic reasons—for example, comments in an interview that discouraged them from continuing with the application process.

Here are some statistics from some of the best-known cases alleging a pattern and practice of employment discrimination:

1. In a suit against T.I.M.E. Freight Company and the Teamsters' Union, the plaintiffs showed that of 6472 employees, 5% were black, and 4% were Hispanic. Of the 6472 total employees, 1828 were line drivers, the highest paid position; of these line drivers, 0.4% were black, and 0.3% were Hispanic. Employees in the lowest paid divisions, city operations and service, included 83% of the blacks employed by the company, 78% of the Hispanics employed, but only 39% of the whites employed (10),

2. In a suit against Local 28 of the Sheet Metal Workers' Union, the local serving metropolitan New York City, the plaintiffs showed that 3.9% of union members were black, compared with an estimated 29% of blacks in the relevant labor pool (11).

3. In a suit against Duke Power Company, the plaintiffs showed that 34% of the white males in the relevant labor pool (in North Carolina) had high school diplomas, but only 12% of the blacks did. The Court concluded that it was prima facie discriminatory to require a diploma for employment, without any further explanation of its job-relatedness (12).

4. In a suit against the Lackawanna, NY, plant of Bethlehem Steel, the plaintiffs showed that 20% of newly hired white workers, but 50% of newly hired black workers, were assigned to work in the coke ovens, the hottest and dirtiest departments at the plant. Seniority and transfer policies then combined to lock black employees into their original department of hire (13).

5. Lest it be thought that these cases are merely of historical interest, compare this to the situation involving firefighters in the city of Chicago. As of 1974, only 4% of Chicago firefighters have been black and only 0.5% Hispanic, figures that had persisted since the 1950s, although nearly a third of the city's population were black. In 1986, it was still the case that only 2.6% of firefighter captains were black, and only 1% were Hispanic, despite the fact that by this time a majority of the city's population were black. Just last year, the Seventh Circuit, in an opinion authored by Judge Posner, concluded that an affirmative action plan for promotions was justified, given the city's history of discrimination (14).

Now compare with these cases successfully alleging employment discrimination, some of the recent data concerning differences in treatment by race. The question to bear in mind is whether these statistics are sufficiently parallel to the employment statistics, so that they would at least look analogous to a prima facie case.

1. A Duke University study of patients with obstructive coronary disease showed marginal differences between blacks and whites in the rates of angioplasty, but significant differences in the rates of bypass surgery. Controlling for such factors as age, sex, disease status, comorbidities, date of treatment (between 1984 and 1992), and insurance status, blacks were 32% less likely to undergo bypass surgery than whites, and 35% less likely to undergo any revascularization procedure at all. Yet blacks had a higher five-year mortality rate overall (27% compared with 20%) (15).

2. A sample of the Medicare population receiving primary total hip replacement between 1986 and 1989 revealed that blacks were 53% as likely to receive the procedure as whites (16).

3. A study of mammography rates among black and white women enrolled in the Medicare program in ten different states revealed that black women had mammography at just over half the rate of white women (9% to 15%). These differences persisted, controlling for age, income, and frequency of visits to primary care physicians (17).

4. A study of the use of bone marrow transplantation in leukemia and lymphoma showed that, controlling for factors such as disease type and

> insurance status, black patients were 51–53% as likely as whites to receive transplantation for leukemia, and 34–45% as likely to receive transplantation for lymphoma. This study was conducted from hospital discharge records in the states of California, Massachusetts, New York, and Maryland, for the years 1988 and 1991 (18).

To be sure, there may be many explanations for these differences in the use of treatment. Each of these studies controls for certain obvious differences, such as insurance status, disease severity, or comorbidities. One might hypothesize many further explanations for the differences that are not captured by such variables. Black patients may be more suspicious about the motives of health care providers, particularly when highly interventionist or expensive forms of care are offered; given the legacy of Tuskegee, such suspicions would not be surprising. Black patients may prefer less aggressive forms of care. There may be resistance to technologies such as X-rays used in mammography. All of these would be nondiscriminatory reasons for the differences, at least on the surface. All I am contending is that these data are comparable to the data used in lawsuits alleging a pattern of discrimination to establish a plaintiff's prima facie case. If the data are significant in this way, the burden should then fall on the health care professions to examine further what explanations might be offered for the differences, and to inspect carefully whether the explanations are benign or conceal aspects of discrimination in one respect or another.

Indeed, the authors of these studies do suggest the need for further investigation. The authors of the study of coronary revascularization procedures, for example, observe that race may only be a surrogate for other socioeconomic factors not captured by their demographic information, such as family support structures. Patient preferences may also play a role. The authors caution that further investigation is necessary to explore the possible relevance of such factors. At the same time, however, they observe the need to consider whether subtle factors in the physician-patient relationship are also affecting patient utilization of therapies: ". . . we did not have access to information on the patients' preferences regarding therapy. Future investigations must clearly be directed at determining how patients assess the risks and benefits of cardiac interventions and how their interactions with physicians may affect that assessment." (15).

This observation might be put in the structure of an employment discrimination lawsuit, in the following way. The data about different rates of use of therapy by race establish a prima facie case of discrimination. The burden then shifts to health care providers to explore whether there are legitimate, nondiscriminatory explanations for the differences. It appears that there may be: differences in patient preferences, in patient attitudes toward the health care system, and in the more subtle demographic factors that support patients undergoing difficult care regimens. Whether such explanations are forthcoming, of course, at the present time requires further investigation. But suppose that they are; this still would not end the matter. For the burden then shifts back to those alleging discrimination to show that the apparently nondiscriminatory explanations are pretextual. And here, too, there are issues worthy of investigation. Suppose, for example, that a white physician offers mammography to a black woman. She refuses. He accepts the refusal without further comment. Perhaps he accepts all such refusals from patients without comment, but perhaps race matters in the encounter. The physician may be able to work in more encouraging ways with his white patients to enable understanding of the reasons for the recommendation of mammography. He may be able to allay their fears more successfully. He may have a better or more sympathetic understanding of what lies behind care refusals from his white patients. Or, he may be a little more willing to believe that black women are less likely to accept mammography anyway, so further discussion would be a waste of his time. In short, what I am suggesting is that the burden of proof lies on the medical profession to investigate further the explanations for the differences in utilization, and then to at least consider whether these explanations in turn mask problematic effects of race.

Two final observations are worth making. First, although these studies were all published in major medical journals, they appear not to have drawn journalistic interest. LEXIS searches I have conducted indicate that although the *New York Times* reports regularly on medical research, none of these studies was reported in the *Times* when it appeared. Indeed, racial variations in the use of health care have not been much reported by the *Times*. In 1997, only three of the stories concerning health care that appeared on the front page of the Sunday edition raised issues of race. None of the stories by Gina Kolata, a frequent reporter on health care issues, raised questions of race; only two of the "Personal Health" columns by Jane Brody noted race as a factor in the occurrence of health conditions. Only one story by Lawrence Altman, on improved blood pressure control and the reduction in stroke deaths, noted differences by race. Treatment of HIV was a notable exception; in 1997, the Times ran significant coverage of a study by Columbia University's School of Public Health showing significant differences in access by race to combined drug therapies. This lack of journalistic interest, I would suggest, both fails to raise the issue of the need for further research, and fails to educate patients and the health care community about important aspects of the distribution of health care.

Second, even if ultimate investigation of the differences in the use of health care by race reveals nondiscriminatory explanations, this only pushes the question of affirmative action back a step. To be sure, affirmative action would not be justified on the basis of the need to correct ongoing discrimination. But racial differences in the receipt of care, and in resulting health outcomes, would remain. As I indicated above, redistributive arguments for affirmative action were part of the original justification for the Civil Rights Act of 1964; health care is an important opportunity good and thus there are reasons for concern when one group in society fares worse with respect to care utilization and outcome. "Affirmative action" includes a wide variety of positive steps to try to ameliorate racial differences, including education. Suppose it does turn out that blacks are less willing to opt for interventionist care because they are more suspicious of the health care system and more reluctant to experience encounters with it. The appropriate responses might be efforts to dispel the suspicions, to increase levels of comfort with health care encounters, and to educate black patients about what care involves and why it might be helpful —in short, all forms of affirmation action.

IV. Conclusion

Health care is an important opportunity good. Arguments for affirmative action include compensation, correction, and redistribution. In an employment discrimination lawsuit seeking affirmative action as a corrective remedy for a pattern of ongoing discrimination, the plaintiffs would allege statistically significant differences by race, thus shifting the burden of proof to defendants for a nondiscriminatory explanation; if a nondiscriminatory explanation is presented, the burden would then shift back to the plaintiffs to show that the explanation is merely pretextual. Several recent studies of patient utilization of health care by race appear to show statistical differences by race that, were they offered in an employment case, would be sufficient to shift the burden of proof to defendants for a nondiscriminatory explanation. Further research is imperative to improve our understanding of the differences in utilization of care by race. It is also important to consider whether explanations such as difference in patient preferences by race reflect subtle differences in the nature of encounters with the health care system and, if so, to take affirmative steps to reduce these differences. Equality of opportunity requires no less.

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Trust, Patient Well-Being and Affirmative Action in Medical School Admissions

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Abstract

This article reviews the current legal arguments for and against affirmative action in medical education. It concludes that many of the traditional legal defenses for race-based admissions are imperiled or defunct. The author suggests that the best and probably most viable justification for affirmative action policies is the one that recognizes that racial diversity in the medical profession is important because it provides the physicians with whom minority patients can feel safe and comfortable. Trust is a central component of the doctor-patient relationship and is the prerequisite, in many cases, to the individual physician's ability to practice good medicine. Unfortunately, minorities' historical and current experience with the medical profession and health delivery system frequently breeds suspicion rather than faith. As a result, society and the medical profession have a compelling interest and duty to produce physicians who can inspire trust in patients. In the short-to-medium term, race-conscious admissions policies may be necessary to fulfill this duty. **Key Words:** Trust, affirmative action, racial prejudice, medical education.

Jordan Cohen, President of the Association of American Medical Colleges (AAMC) (1), recently predicted increased attempts to overthrow affirmative action programs nationwide and encouraged those associated with medical education to "beat back attacks on affirmative action in higher education wherever they surface." Cohen's concern is well founded. A growing number of federal court decisions have undercut the legal position of educational institutions that wish to use race-based criteria to shape their student bodies. Advocacy groups have fashioned a well-organized strategy to attack affirmative action legally and politically on a national scale. Three universities and their law schools have now been sued by non-minority individuals who claim that they have been wronged by affirmative action policies. Voters in two states, California and Washington, have banned the use of race in university and professional schools' admissions policies through popular referendums. Numerous state legislatures have considered bans on affirmative action in the face of what appears to be declining public support for the practice (2–5). Opponents of affirmative action have yet to make medical education the focus of their attention. But a direct challenge to medical schools' long commitment to affirmative action policies seems to be on the horizon. Indeed, nationally syndicated columnist Jeffrey Jacoby has attacked the practice (6), claiming that "The cost of medical affirmative action isn't theoretical. It is paid in human suffering—sometimes in human lives." Thomas Sowell has condemned affirmative action in medical education as a "self-justifying fraud" that endangers patients (7).

The fervor and increasing prevalence of such charges confirm the urgency of Jordan Cohen's call for a reinvigorated defense of affirmative action programs in medicine. There are a number of ways in which one might defend affirmative action in medical schools, as well as in other con-

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texts. Those arguments, to the extent that they are honest and effective, should be nurtured. But many traditionally sound "legal" justifications for the practice are either disappearing, or are under attack. As a result, the strongest legal defense of affirmative action is likely to be one that refurbishes and renews the claim that diversity is central to the goal of medical education because it is central to the goal of medicine—better patient care. Unfortunately, as Christopher Edley, former special counsel to President Clinton (8), has noted, supporters of affirmative action in the past have been too quick to rely on diversity arguments with little or no explanation. This oversight has limited its utility as a legal and political justification. Some courts, too, have significantly weakened the constitutional viability of the diversity justification. Despite these comments, a review of existing case law suggests that a reconstruction of the diversity concept and its role in medical education is more likely to survive constitutional scrutiny than other strategies (9).

The Law

Current constitutional jurisprudence and escalating private litigation are endangering affirmative action policies nationwide. In 1994, in Podberesky v. Kirwan, the 4th Circuit Court of Appeals held that the University of Maryland's race-based scholarship program was constitutionally impermissible (10). The 1996 Hopwood v. Texas 5th Circuit Court ruling made it virtually impossible for educational institutions in Texas, Louisiana and Mississippi to take race explicitly into account in their admissions decisions (11). In late 1998, the First Circuit Court in Wessman v. Gittens prohibited the prestigious Boston Latin School's affirmative action policy, a practice in place in part because the institution had once practiced racially discriminatory policies (12).

Legal challenges to affirmative action policies are primarily based on the "equal protection" clause of the 14th Amendment of the U.S. Constitution. The 14th Amendment stipulates that "No state shall . . . deny to any person within its jurisdiction the equal protection of the law." The equal protection clause applies not only to state laws, but also to the policies and actions of state agents and state institutions. Actions involving classification, differentiation, or discrimination based on race must meet an especially high, court-designed test—the "strict scrutiny test." Under the strict scrutiny test, the challenged state classification is presumed to be unconstitutional and invalid unless the state entity can show that the racial classification or action is necessary to further a "compelling state interest." In addition, the state must show that the state action in question is "narrowly tailored" to further the compelling state interest; that is, the state must consider: (1) the efficacy of alternative remedies; (2) the flexibility and duration of the policy; (3) the relationship between the program's numerical goals and the percentage of minorities in the relevant population; and (4) the impact of the program on the rights of third parties (13).

The courts have adopted this high standard in view of the history of legal discrimination against African Americans, and use it to strike down nearly any state action that discriminates "against" minorities (14). Legal scholars and judges agree that the strict scrutiny test is appropriate for state actions that have the effect or intent of "harming" minorities. Many, however, argue that a more permissive standard should be applied to state action that is intended to "benefit" minorities (15, 16). For example, if courts used the "intermediate-level-of-scrutiny test" to judge the constitutional validity of state actions intended to benefit minorities, programs like affirmative action would be more likely to pass constitutional scrutiny. Supreme Court rulings on the issue remained inconclusive until Richmond v. Croson (1989) and Adarand Constructors, Inc. v. Pena (1995), which held that racial classifications used for affirmative action purposes must meet the same strict scrutiny test that is applied to other racial classifications (17, 18). It is possible that future federal judges and supreme court justices will reevaluate the standard of review that should be applied to state action intended to benefit minorities. But for now, medical schools and other state institutions must pass the strict scrutiny test when attempting to aid minorities with race-specific actions (19, 20).

The Law of Bakke

Given the current state of affirmative action jurisprudence, what must a medical school or legislature do to justify affirmative action practices and policies designed to increase African American and other minority enrollment in medical schools? There are some fairly clear guidelines. Medical schools cannot have explicit quotas or set-asides based on race. For example, some schools may have a "rolling admissions" policy that sets aside a number of reserved seats for particular racial groups, perhaps linked to the percentage of the minority in the state, region or nation. This is the kind of practice that Regents of University of California v. Bakke (1978) rendered constitutionally unacceptable (21), even though it might be defended on the grounds of policy or justice. Neither can a medical school have dual admissions committees or attempt to attract minority matriculants with race-based scholarship programs (10, 11).

Although these forms of affirmative action are almost certainly prohibited, Justice Lewis Powell explained in Bakke that race could be permissibly used as one "plus-factor," among others, in admissions considerations. For example, admissions committees may weigh considerations such as geographic origin, maturity, civic contribution, leadership potential, relevant work experience, as well as grades and standardized test scores, in order to achieve intellectual diversity. According to Bakke, race may also be considered one of these plus-factors as long as the race of the applicant does not prove to be the "decisive" or determinative factor in the decision to admit the student (21). While this principle emanated in the Bakke case is under attack by some, it has been widely accepted for two decades. This policy gives admissions committees some flexibility in their admissions deliberations to increase cultural and intellectual diversity in their student bodies.

But Bakke does not give admissions committees a free hand when considering the race of those who will matriculate at their institutions. If race as a plus-factor is determinative in individual cases, those cases must face the strict scrutiny test if challenged by a disgruntled non-minority applicant. The Center for Individual Rights, an activist anti-affirmative action group, has produced and distributed a detailed handbook to aid applicants who feel they have been treated unjustly (22). The handbook encourages prospective students to be "skeptical" of claims that race is used only as a plus-factor, and identifies what it deems "suspect" admissions practices. In addition, it provides detailed guidance on how non-minority applicants can discover and demonstrate whether an institution is using race as a determining or decisive factor in its admissions decisions (23). Individuals, through the various states' freedom of information acts, can gain access to a wide range of information, including school policies, application files, minutes of meetings, worksheets and correspondence (24, 25). The applicant pool's racial make-up, GPAs, standardized test scores, residency and other variables can be evaluated using common statistical techniques, in an attempt to determine whether race played a decisive role in the institution's decision to admit students.

If an individual challenging a medical school's admissions practices can demonstrate, through statistical summary or otherwise, that race has played a determining role in decisions to admit students, then the burden shifts to the institution to defend its admissions practices. If the medical school can prove that the non-minority applicant would not have been admitted, even in the absence of race-conscious practices, the challenge will fail. However, it may sometimes be difficult for institutions to make such showings, given the difficulty of proving a negative (i.e., that the applicant would not have been admitted) and the excellent qualifications of the students likely to be chosen as lead plaintiffs in anti-affirmative action cases. In order to justify its practices, the medical school would then have to defend its admissions practices according to the strict scrutiny test. By this test, an admissions practice that is shown to use race as a determining factor will be presumed to be unconstitutional unless the medical school demonstrates (1) that the policy or practice is motivated by a "compelling state interest" and (2) that it is narrowly tailored to achieve that state interest.

Discrimination

Courts have agreed that the intent to remedy the effects of discrimination represents a "compelling state interest" under the 14th Amendment. However, medical schools will likely have difficulty defending race-based policies on these grounds. The Supreme Court has definitively declared that the intent to remedy the effects of general "societal" discrimination, racism and prejudice is "not" a compelling state interest. Instead, to justify a race-based remedy, policy makers must precisely identify specific acts of past or current discrimination by state institutions or actors (26, 27). This test was applied exactingly in Hopwood (28), which held that racially based programs at a state professional school could only be justified if there was evidence of the effects of discrimination "by that institution." If the Hopwood approach prevails, it will be virtually impossible for medical schools to justify affirmative action practices based on the effects of past discrimination. Most medical schools have long-standing commitments to affirmative action and have long since abandoned explicitly discriminatory policies (29, 30).

It is possible, however, that other courts will not accept the Hopwood formulation and may allow medical schools to demonstrate that their policies are intended to remedy the continuing effects of discrimination that have occurred throughout other units in the relevant state's public education system. State institutions of higher learning are linked directly to the state's primary and secondary educational system. Consequently, it seems reasonable to allow medical schools, professional schools and other institutions of higher learning to remedy the continuing effects of past discrimination in K–12 years of the same school system (28).

Even this approach will pose difficulties to medical schools defending challenged affirmative action practices. Medical schools established policies years ago under the assumption that the use of race as a "plus-factor" was constitutionally permissible in order to create a more diverse educational environment (21). These schools did not base their affirmative action programs specifically on an attempt to remedy past discrimination, even though that was almost certainly an additional goal of these programs. Consequently, medical schools and policy makers probably never collected specific evidence of the effect of racial discrimination or attempted to explicitly link their remedial policies to the harms generated by racial discrimination. That evidence will probably be difficult to collect after the fact (31). It may be similarly difficult to provide courts with evidence of discrimination against the minority students currently applying for admission to medical schools. Most of the students now entering medical school were educated in a public school system substantially cleansed of "overt," state-mandated discrimination (32). Although discrimination in a number of guises continues to harm minorities in society, and perhaps in the educational system, such discrimination may not be easily demonstrable or linked to official state policy. Moreover, such evidence, if collected retrospectively in order to justify medical school affirmative action policy, may not be accepted by the courts. According to Christopher Edley, the "issue of post hoc evidence is critical" because many practices and programs were adopted without detailed evidential findings and it would be politically impossible to re-legislate now (8).

Racism and discrimination continue at the societal and institutional levels and may justify remedial action. However, law and morality are not always consonant. The type of discrimination required to support remedial action has ironically been swept away by legally mandated desegregation and relatively aggressive civil rights enforcement regarding public education. Racial discrimination is more likely to manifest itself, for example, in a racially hostile or insensitive educational environment rather than in flagrant *de jure* educational segregation and deprivation. Therefore, if medical school affirmative action policies are to survive the strict scrutiny test, another foundation for the state's compelling interest in increased minority enrollment must be crafted and championed. Although the concept of diversity in medical school education is underdeveloped and under attack legally, it is the most promising constitutional defense of affirmative action in medical education.

Diversity

The most important discussion of diversity as a constitutional justification for race-based admissions appeared in Bakke. Justice Powell declared that the University of California at Davis medical school's desire to create a diverse student body in order to provide more physicians for underserved minority populations did not constitute a compelling state interest sufficient to meet the strict scrutiny test. Powell (21) did not declare that providing physicians to underserved populations could never constitute a compelling state interest, but only that there was "virtually no evidence in the record indicating that petitioner's [the medical school] special admissions program is either needed or geared to promote that goal."

Powell's opinion leaves open the possibility that, given sufficient evidence, increased minority admissions might be deemed integral to increasing the number of physicians to care for underserved populations and thus might qualify as a compelling state interest. But medical schools never needed to employ this defense. There was another reason why the diversity justification might be considered a compelling state interest. Diversity, according to Powell (21), was a compelling state interest because it was vital for the "robust exchange of ideas." Powell's articulation of the diversity justification provided medical schools with the justification they required to pursue in good faith affirmative action practices based on race (33). The constitutional meaning of diversity in higher education remains a rarely discussed concept in case law and has never again been analyzed by a Supreme Court majority opinion. This lack of judicial analysis has undermined the diversity justification, as affirmative action programs face more frequent legal challenges.

The diversity justification was attacked directly in University of Texas v. Hopwood (11). The Hopwood opinion claimed that Powell's elevation of diversity as a compelling state interest in Bakke was never joined by the majority of the court and, as a result, did not represent the position of the Supreme Court. The dissenters in Hopwood predicted that the "radical implications of this opinion, with its sweeping dicta, will literally change the face of public educational institutions throughout Texas, the other states of this circuit, and this nation (34, 35)." But the implications of Hopwood outside the Fifth Circuit are unclear. University of Texas v. Hopwood (11) is not the law of the land anywhere except the 5th Circuit. Bakke is. Besides Bakke, there are a number of important references to the diversity justification scattered in Supreme Court opinions (27). Even so, the diversity justification for educational affirmative action policies is clearly in need of revitalization.

Future courts may accept diversity as a compelling state interest if the justification is carefully articulated and supported by evidence provided by the legislatures or relevant governmental institutions. The special requirements of the doctor-patient relationship, the nature of race relations in the U.S. and the data that has become available in the last 20 years may help convince courts (and perhaps the public and legislatures as well) that diversity is a constitutionally legitimate motivation for enacting an affirmative action program. Diversity might be considered a compelling state interest in medical education for at least three reasons: (1) to increase the number of physicians who treat traditionally underserved patients and specialty areas; (2) to promote the robust exchange of ideas in medical education; and (3) to render better medical care to minority patients by providing them with physicians whom they can trust.

More Care for Underserved Patients

Unlike in Bakke, there are now studies that help document that minority physicians care for a greater percentage of minority patients than do their white counterparts. Equally important, minority physicians more frequently serve communities with an insufficient number of physicians and care for a greater percentage of Medicaid and uninsured patients (36–40). These studies provide evidence that minority physicians benefit society as a whole by caring for populations that may otherwise lack sufficient medical professionals. Medical schools might supplement these studies with information gleaned from their own graduating classes. States have a compelling interest in improving the health of their citizens. Thus, a medical school might argue that affirmative action programs that produce more physicians for underserved communities serve a compelling state interest.

Even if courts view increasing minority physicians as a way to improve the health of underserved populations, challenged programs would still have to meet an additional constitutional test: that the race-conscious measures are "narrowly tailored" to accomplish those goals. The defendant medical school would have to satisfy the finder of fact (court or jury) that the policy was reasonably limited in time and scope, that the cost to third parties had been calculated and was reasonable, and that there existed no race-neutral means to reach the same ends.

Are there race-neutral incentives that a state and its medical schools could use to bring physicians and healthcare to underserved regions? While the answer to this question is not immediately clear, it is a question that might have to be resolved if a medical school attempts to defend affirmative action policies on these grounds. Similarly, there may be race-neutral ways to increase the number of primary care physicians, the other apparent benefit of increasing the number of minority medical students.

But such a defense of diversity is disturbing on other grounds. Many minorities choose to serve underserved and sometimes remote populations as primary care practitioners. However, many minority physicians wish to follow other professional routes, for reasons of intellectual excitement, higher financial rewards or personal taste. That clearly is their right and society should be wary of a policy that suggests that African Americans be directed to specific demographic, geographic and economic strata of medical practice. This caveat does not necessarily mean that increased service to underserved groups cannot be used to help justify affirmative action policies. But the questions concerning this approach suggest that other defenses to diversity should be explored as well.

Cultural and Intellectual Diversity

Powell also explained in Bakke (21) that diversity may be a compelling state interest because it leads to a "robust" exchange of experiences, outlooks and ideas that enrich the professional school and "better equip its graduates to render with understanding their vital service to humanity." Diversity, he suggested, helps students develop better interpersonal skills by allowing them to interact with people of different perspectives and "communicate across the boundaries they create." Thus, a diverse medical student population provides more than mere intellectual enrichment; it serves the practical function of better preparing non-minority medical students to care for an increasingly diverse patient population.

Minority medical students can help non-minority medical students understand the racially and culturally based concerns of minority patients.

Diversity in the educational arena is frequently defended as a means to enrich the intellectual experiences of students. However, the goal of better patient care is a far more compelling argument constitutionally than mere intellectual excitement in the classroom. And if an affirmative action policy is challenged legally, or even politically, evidence that such gains occur would be of vital importance. Again, such evidence may be difficult to acquire. Moreover, even if a court does agree that better patient care for minority populations represents a compelling state interest, the defendant medical school would have to show that its policy was "narrowly tailored" to serve that particular goal. The policy would have to be limited in scope and duration, and the school would be asked to show that it had considered race-neutral means of accomplishing the same goals. Are there textbooks that would aid in training non-minority physicians to thoughtfully care for their minority patients (41)? Would workshops, discussion groups, speakers or the use of standardized patients be sufficient, without resorting to race-based admissions practices (42)? Medical schools that defend their affirmative action policies on the grounds of better preparing their non-minority students for medical practice would be well advised to prepare answers to these questions in the event that their polices are challenged.

Like Doctor, Like Patient

The third reason that diversity in the medical profession is a compelling state interest is that it is the most certain way to assure that minority patients will receive adequate health care. The state has an interest in the effective delivery of health care to all segments of the population. As a result, the state assumes a concomitant interest and duty to train physicians who can engage in mutually trustworthy therapeutic relationships with their patients. Minority groups, especially African Americans, have had a different historical experience with the medical profession than have non-minority patients. As a result, suspicion and misunderstanding, rather than trust, communication and empathy, seem to characterize many medical encounters between physicians and patients of different races or ethnic groups.

African American suspicion of the medical profession, Annette Dula has argued (43), "cannot be simply written off as paranoia or hypersensitivity." It has its roots in antebellum culture and continues into the present. Slaves could not reject or control health care and had limited control over their bodies (44). In addition, they were used as experimental subjects for painful and dangerous pharmacological and surgical remedies (45). These abuses instilled in the African American community a mistrust of the white medical profession that prevailed long after emancipation. Many in the medical profession subscribed to and developed 19th-century racial theories supporting the view that blacks were physically and mentally inferior to whites (46). Racism and race-based misconceptions regarding African American biology and physiology led to the infamous Tuskegee syphilis study, which continued in plain view of the white-dominated medical and scientific communities for more than forty years (47, 48). In addition, the bulk of the white medical profession acquiesced in, or actively advocated, the continuation of the formal and informal segregation of the health delivery system, a system which frequently delivered patently unequal care (49). The persistent legend that Dr. Charles Drew, a black pioneer in transfusion research, died after an automobile accident when he was refused "white" blood reflects the grim reality that generations of African Americans suffered and died because they did not receive adequate medical services in a segregated medical world (50). This continuing suspicion and skepticism has undermined the trust that should be central to the doctor-patient relationship.

Minority distrust of the medical profession is also related to their experience with the contemporary health care system. It is widely acknowledged that minorities, especially African Americans, have less access to health care services, higher mortality rates, and greater disease rates for a wide range of illnesses (51). While many of these disparities may be explained by differential socio-economic status, there is an extensive and growing literature that strongly suggests that stereotypes, prejudice and racism may still influence the medical care provided to minorities (52). There are studies that suggest that physicians treating minority patients are "less likely to follow guidelines from nationally recognized organizations for health promotion and disease prevention" than are physicians who care for predominantly white patients (53, 54). Other research reveals lower utilization rates for African Americans for ordinary components of basic medical care and reports that African American patients are more likely to feel that physicians failed to give them full information about their diagnosis, treatment and follow-up (55–57). Other studies have found that African Americans are more likely than whites to be hospitalized for avoidable conditions (58), may receive a lower quality of care when hospitalized, and show more instability at discharge than do other patients (59, 60). African American patients receive fewer hip and knee replacements (61), are less likely to receive prophylactic therapy for HIV (62), are less likely to undergo surgical resection for colorectal cancer (63), and are less likely to receive angiography, angioplasty and coronary artery bypass surgery than white patients (64 – 69). In contrast, African Americans appear more likely to receive procedures patients typically wish to avoid, lower-limb amputation, bilateral orchiectomy and cesarean delivery (70). These racial disparities persist, in many cases, after controlling for social, economic and medical factors, leading many medical scholars to believe that some form of prejudice or bias may be at work (71, 72). The authors of one racial disparity study (73) concluded that their findings "suggest inappropriate influences on clinical decision making that would not be addressed by changes in reimbursement." Another commentator noted that the treatment disparities in cardiac care raised the "probability" of "covert or unconscious racial stereotyping by physicians (52). The *New England Journal of Medicine* recently reported a study involving standardized patients that found that the race of the patient independently influenced the diagnosis and treatment recommendations of the physicians. The authors concluded (74) that such findings "may represent overt prejudice on the part of physicians or, more likely, could be the result of subconscious perceptions rather than deliberate actions or thoughts."

The Role of Trust

Physicians require the trust of patients in order to treat them effectively. According to Edmund Pellegrino (75), trust is a central component of medical professionalism:

> Those in need must trust that their vulnerability will not be exploited. Professionals must invite that trust because without it, they cannot obtain the information they need to provide assistance or the sanction to undertake delicate and dangerous procedures that put body, property, or spirit at risk.

Unfortunately, the suspicion born of historical experience, the growing empirical evidence showing differential treatment and disparate results, and scattered and common anecdotal accounts give minority patients tenable grounds on which to question the good will and color blindness of white medical practitioners. These suspicions, whether true or not in any individual case, can thwart the doctor-patient relationship, which should be based on trust and the expectation that the physician will act in the best interest of the patient.

Minority distrust of the medical profession may also affect the health of African Americans by influencing such factors as patterns of compliance, preventive care, and patient disclosure of information and choice of therapies (43). For example, one study found that African Americans believed that racism was a key reason that black health indicators consistently lag behind those of whites (76). As one African American publication (77) states, "black distrust of the medical community runs deep." Mistrust of the medical profession is a commonly cited reason why African Americans frequently hesitate to donate organs or complete advance directives (78). Viola Clark-Goodwin, a community health worker, warns African Americans that "Stereotypes and assumptions need to be put in their place. Don't fall for any doctor telling you that you look a certain way, therefore, you should be or must be a certain way. Question every specialist's opinion regarding your health." Clark-Goodwin (79) advises African Americans to "seek out a friend or a peer you can trust, someone of your own ethnicity, someone who speaks your language." African Americans should not be forced to rely on friends and peers for medical advice and comfort. They should be able to rely on trained physicians.

The foregoing comments suggest that this suspicion is so deep-seated and widespread that, in the short term, the only remedy is to provide minority patients with physicians with whom they will feel safe and comfortable. Not surprisingly, minorities, when asked, usually prefer to be treated by physicians from their own ethnic groups (80). As former U.S. Secretary of Health and Human Services Louis Sullivan recently observed (81), the country has a "social and moral obligation to cultivate physicians who can relate to that segment of the community." Building on Sullivan's premise, it should be possible to craft and support an argument that the state has a compelling interest in producing physicians who can treat its citizens effectively. Some federal courts have recognized the utility and importance of diversity in law enforcement agencies that are charged with working with diverse populations (82). Like physicians, law enforcement officers must possess the trust of the persons in the community they serve in order to get the information, compliance and legitimacy they require to do their jobs appropriately.

It is unclear whether courts will accept the need to produce more physicians of color as a reinvigorated justification of diversity and as a compelling state interest. But it will likely be easier to collect evidence in defense of diversity than to prove that affirmative action policies are required in order to remedy the effects of past or current discrimination. There is abundant evidence that minorities have a fundamentally different experience with the health care system than do majority patients. Further studies investigating disparate treatment and minority patient preferences and fears would be central in demonstrating the state's interest in a diverse medical profession. Qualitative and quantitative evidence demonstrating the impact that racially diverse health care teams have on patient comfort and trust would also buttress this argument.

Regarding Merit

One of the central attacks on affirmative action is focused on the assertion that preferential policies undermine the democratic ideal of advancement based on merit. Moreover, critics of affirmative action claim that acceptance of less meritorious candidates into medical schools has human costs in the form of less qualified physicians. As Jeffrey Jacoby contends (6), "Minority communities and poor families don't need black doctors. They need good doctors." It is possible, of course, that they could need both. Merit-based attacks on affirmative action are fueled by the fact that African American median MCAT scores and GPAs are frequently lower than those of white medical school matriculants (83).

Merit seems to have two meanings in the context of admissions to medical schools: (1) that individuals "deserve" admission as a reward for performance of some sort; and (2) that individuals should be chosen for particular roles or endeavors because their qualifications are evidence that they are better suited to fulfill the job requirements than other individuals (84). There appears to be a widespread assumption that a strict, competitive meritocracy preceded the affirmative action efforts of the last 30 years in professional schools. That, however, is not the case. MCAT scores were introduced in the 1950s, not to predict who would be the best physicians, but rather to reduce the attrition rate that had ballooned as a result of relatively open (for whites) admissions policies at most medical schools. As the pool of well-prepared students increased in the 1960s and 1970s, competition for admissions slots increased. The mean MCAT score of matriculants rose accordingly, beyond what was necessary to guarantee reasonably successful completion of a course of medical studies (85). Thus, while such criteria as MCAT scores and GPAs are frequently taken as objective measures of which students will be the better physicians, they were instituted by the medical education establishment for entirely different reasons, i.e., to ensure that matriculants could successfully complete a rigorous course of study. Recent studies have confirmed that students with lower MCATs and GPAs who receive admission preferences sometimes struggle in the basic science courses and are more likely to retake the U.S. Medical Licensure Examination (USMLE). However, they graduate at virtually the same rate as non-preferential matriculants and receive similar evaluations from residency directors (86). There is no empirical evidence that matriculants with lower test scores turn into inferior doctors and provide inadequate health care for their patients. Thus, as designed, such measures serve as an efficient and objective predictor of who will be able to complete the course of study. But they do not appear to be accurate evidence of how well a particular individual can perform his or her required professional function—taking care of patients.

What then are relevant indicators of merit, of which applicants are better suited to fulfill the duties of a practicing physician? GPAs and MCAT scores clearly provide relevant information. But are there other important considerations? Some observers reason that minority physicians increase the "user friendliness" of the health care system and the trust of the minority patient population, thereby increasing accessibility. Minority practitioners may also prove more "culturally sensitive to their populations and organize the delivery system in ways more congruent with the needs of minority populations." (40). As Louis Sullivan has explained (87), "Attitudes such as understanding the patient's culture, empathy for the patient, and integrity of the physician inspire trust, and a combination of science and art are important because medicine involves the most personal kinds of decisions we can make." Thus, those critics who claim that race-conscious admissions policies undermine or scorn merit appear to miss the point. In short, an affirmative action argument based on patient-well being "is" a merit-based argument, in that race may be directly related to the medical school applicant's ability to practice good medicine. It may be difficult to measure the impact and patient benefit of increasing the number of minority physicians, but it is reasonable and fair to deduce that such benefits will accrue. It is also fair to weigh those benefits against the potential costs of affirmative action programs. Although this will be a difficult and uncertain calculation, its solution could play a critical role in defending affirmative action policies, legally and politically. The costs of such programs, if considered honestly and soberly, are likely to be outweighed by the promise of providing better care for all patients.

Conclusion

Medical schools should use all viable arguments in order to defend legitimate and well-designed affirmative action practices. If institutions can demonstrate that their policies are justified on the grounds of remedying the effects of past or current discrimination or distributive justice, they should do so. In the current legal and political environment, however, these arguments will be less likely to win judicial support than ones based on the state's compelling interest in providing sufficient medical care for its citizens by increasing the diversity of the physician population. Moreover, a carefully restated diversity argument, for a number of reasons, will be more likely to win the minds, if not the hearts, of the public and thus pacify at least some of the political opposition to affirmative action in higher education.

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Issues of Health Care Mistrust in East Harlem

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Abstract

Barriers to the delivery of health care services to the Latino community are described and analyzed. Fear of deportation, unfamiliarity with modern medicine, inability to speak English and reliance upon traditional curing practices all contribute to the harmful underutilization of medical services which we see in the Latino community. Health care providers who serve that community need to overcome these obstacles by expanding their cultural awareness and increasing the effectiveness of their communication. **Key Words:** Latino, Hispanic, health care, East Harlem, folk medicine.

I WILL BEGIN THIS PORTION of our conversation by speaking to today's multicultural reality which impacts on both the delivery and the reception of health care in the United States. My remarks are grounded in my experience as a community health nurse in East Harlem. They are intended to shed some light on certain conflicts that take place between health care providers and recipients of health care. These conflicts arise out of a climate of distrust and fear. I will begin my remarks by speaking about this general aura of fear and misunderstanding; I will then briefly discuss the role of folk medicine in the community I serve. It is my belief, born out of practice, that respect for the traditions of people from a culture other than the dominant one does a great deal to eliminate mutual distrust and fear, and to foster respect and trust.

As a community health nurse working in East Harlem, I have found that much of the Latino community we serve regards American health care with a great deal of suspicion. Chief among the reasons for this distrust is the fear of deportation among the undocumented. Language barriers and cultural differences can also lead to misunderstandings of the American health care system.

The Hispanic community, which is the fastest growing ethnic group in the United States, consists of people from diverse cultures and ethnic groups. The Latino/Hispanic population in this country is comprised of hard-working individuals who have come here to improve their quality of life. Whether they emigrated, migrated or were born in this country, Hispanics in the United States have retained much of their own culture while trying to understand and adopt many aspects of the American way of life.

The Latino population in East Harlem continues to grow and is currently the largest population that the Little Sisters of the Assumption Family Health Services (LSAFHS) serves. In 1995, 60% of our patients were Latinos; in 1996, that group increased to 65%; and during the last six months of 1997, Latinos comprised 70% of our active caseload (data gathered by LSAFHS). In addition to the number of Hispanics estimated by the U.S. census, there are also significant numbers of undocumented people who have need of health care services but do not seek them. The Latino community is often reluctant to utilize the American health care system. This reluctance is due to lack of income, insurance and legal status, and to cultural beliefs. It is also due to the manner in which the health care system presents itself to this community.

Fear and Misunderstanding

Undocumented Latinos face the constant fear of being investigated by authorities. Although this threat may be unfounded, the fear is certainly a reality. Health care workers are often viewed as extensions of government agencies; thus the fear of deportation and perceived threats to personal security and well-being are very real. There is a great reluctance on the part of undocumented persons

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within the Latino community to seek health care because they fear investigation and exposure of their illegal status. Since the role of the health care provider is to look after a person's well-being, this level of fear and distrust is often misunderstood by providers. We know that this fear and distrust, in relation to health care, is a misguided fear. It is our responsibility to convey truth to clients, in an effort to enhance the trusting relationship.

An example of this is the case of a young woman who received third degree burns on her right forearm while attempting to dispose of hot oil from a pan. Friends instructed her not to go to the hospital, warning that she would be discovered by authorities and deported. Instead this woman sought the care of a curandera, a folk healer, in the neighborhood. She allowed the curandera to perform the painful task of scraping the charred layers of skin and applying a salve to the area. I saw this same woman two weeks after the incident. She had continued to refuse medical care to her forearm in spite of numerous attempts to alleviate her fear of deportation.

The feeling of being misunderstood and disconnected starts, but does not end, with the language barrier. With the influx of newly arrived Latinos to the various parts of the United States, the number of Latino people who have difficulty speaking and understanding English has increased. Some who have lived in the country for a long time are not highly proficient in the English language (1).

I have discussed their missed medical appointments with numerous clients. When I asked them why they missed their appointments, their response was typically—the language barrier. "I don't understand the doctor and he/she does not understand me." Although many of the hospitals and clinics in this community have Spanish-speaking personnel on staff, they are often reluctant to speak their native language in a clinical setting, and these hospitals and clinics often do not think to make use of the special skills of their bilingual staff members. Since it is virtually impossible for a health care provider to establish an adequate therapeutic relationship with a client who speaks little or no English, trust cannot be established. The frustrating noncompliance we frequently encounter is our own doing.

Folk Medicine vs. American Medicine

In most villages and rural areas of Mexico and Latin American countries, the primary sources of medical care are practitioners of folk medicine and midwives. Since this has been the norm in their countries of origin, newly arrived Hispanics usually favor this type of health care over American medicine. Due to the experience and knowledge that the Latino community has brought with it from various countries, I find that there is a greater sense of trust and faith in the folk healers than in the doctors. American medicine, to the outsider, may seem very foreign and at times unnecessary, especially when it is not explained. Most clients I encounter need to be persuaded of the validity and utility of modern medical practices.

Herbal medicine is one of the biggest aspects of folk medicine practiced in various Hispanic cultures. The curanderos(as) have an advantage over American health care providers in that they share the same or a similar culture, tradition and language. There are Hispanics who prefer herbal remedies over prescribed medication because they are all natural. They believe that medicine prescribed by an American health care provider is made of harmful chemicals and therefore toxic to the body. An example of this is an eight-year-old girl with AIDS who is prescribed several medications. Although the purpose and side effects of each medication have been explained to her grandmother, she continues to use herbal remedies for her granddaughter's afflictions instead.

American health care providers tend either to ignore the folk beliefs and practices or try to "educate" their clients by deprecating the folk practitioners. Since available information suggests that the folk methods are often effective, it might well be that a creative cooperation between the two would improve the delivery of health care services (2).

Role of the Health Care Provider

The health care provider must be an empathic listener who is able to understand the client's traditions and values. As health care providers in a Latino dominated community, we have a responsibility to expand our cultural awareness in order to create a client/provider relationship anchored in trust. In turn, this will leave us better equipped to educate future professionals. Our efforts cannot be limited to simply accommodating linguistic differences, although this is an important and necessary task. We need to embrace the client's whole person—their beliefs, traditions and value systems. We must understand and acknowledge their different perceptions of health care.

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Asian Patients' Distrust of Western Medical Care:

One Perspective

Chen-Li Sung

Abstract

Asian patients receive, with significant frequency, suboptimal medical care. The sources of shortcomings in the treatment of the Asian American patient are examined in this paper. I argue that it is mainly a failure to interpret patient behavior correctly which causes suboptimal treatment. Such failure stems not from prejudice, but from a lack of understanding of, much less respect for, the systems of thought about health and illness which form the basis for the traditional or tradition-influenced Asian American patient's approach to illness. "Noncompliant" patient behavior is misunderstood if the physician does not grasp the roots of such behavior in a system of beliefs which is not his own. Misunderstanding begets further "noncompliance," initiating a downward spiral. The way out of such spirals lies, I argue, in seeking a more adequate understanding of the patient's beliefs and their behavioral consequences.

Key Words: Medical philosophy, Asian Americans, distrust, communication skills, medical ethics.

In recent years, the demands of medical practice in a managed care setting have placed increasing pressure on physicians to gain greater yields from less time spent in consultation with each patient. At the same time, the patient population is becoming ever more ethnically diverse, with increases in not only the absolute number of minority patients, but also in the variety of cultures and languages to be encountered. In New York City, the most significant cultural influxes are Hispanic, Asian, and Slavic. Indeed, the Asian immigrant population is itself composed of a myriad of subgroups and cultures, all of which are quite different and incomprehensible even to one another. The Latin population also has a variety of distinct cultural traits, although its subgroups may be less extremely divided than the Asian populations. Suffice it to say that American physicians today confront a multivaried patient population.

This rapidly changing demographic situation compounds the physician's difficulties in providing quality care. The constraints of time and finances are well discussed elsewhere. The limitations placed on the physician's effectiveness because of minority patients' inherent distrust of Occidental medical philosophy, however, are rarely addressed or acknowledged. This often subconscious barrier to full trust between the physician and the patient has dramatic effects on the effectiveness of our health care delivery, particularly in terms of patient compliance. Asian immigrants, in particular, have great difficulties with Western physicians. Their situation merits close examination, both because of the differences between the bases of their distrust and the distrust of other racial groups, and because of the general utility of determining the appropriate physician response to the kinds of distrust which different Asian patient groups exhibit. I will first address what I believe to be the main reasons why Asian patients distrust European medicine, then suggest methods by which physicians can counter their Asian patients' reluctance to believe in our abilities.

Asian immigrants usually come from cultures with long traditions of herbalist or shamanistic healing. The major cultures of Asia, and the

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Chinese in particular, believe in a concept of health based on the flow of energies within the body. The particulars of these beliefs are not necessarily important for this discussion. What is vital in contributing to the Asian patient's distrust of Western medicine is the degree to which this philosophy pervades all aspects of daily life. In most Asian cultures social behavior tends to be centered on the drinking of tea; all medicines are essentially brewed from herbs, which can be appropriately seen as teas for treating specific ailments. To this day, nowhere in the world, except in Asia, do "energy" beverages dominate the soft drink market. The maternal role in promoting daily well-being is particularly focused on the provision of proper nutrients, usually in the form of soups, to cure ailments or simply to promote quotidian wellness. Tiger, rhinoceros, and other animal-based extracts and essences are still in high demand for the same reason. Traditional philosophies upon which Asian concepts of health are based pervade daily life; they are not reserved only for times of sickness. Thus, it is easy to appreciate the feeling on the part of Asian patients that any philosophy of medical practice which is not based in the firmament of energy-flow concepts, is not to be trusted. It is very difficult for Asian patients in general, regardless of social position or education, simply to cast aside large tracts of their cultural heritage in favor of Western scientific concepts, particularly during the vulnerable times of illness.

Asian patients' distrust of the unfamiliar Western health model manifests itself primarily through noncompliance, which can span the continuum from half-hearted medication compliance to total refusal to consult Western doctors. The underlying lack of faith is often expressed as cultural or racial chauvinism. Patients have expressed to me their willingness to receive my advice because I am Asian. They say, "The foreigners don't really know how to treat our illnesses," or, "They don't really know what our illnesses are like." This occurs despite the fact that I have merely repeated exactly what the attending physician just said in English, and where a language barrier was not at issue. These patients believe that disease processes somehow manifest themselves differently in Asians, and that no matter how experienced Westerners may be, they do not comprehend the nature of Asian illness and, therefore, could not possibly treat Asians effectively. Asian patients do not readily accept the inherent universality of Western medical science.

There is, however, a more emotional patient stance behind this rejection of Western medicine. Asian patients sense that when Western physicians ignore Asian health concepts, they are not only dismissing the traditional Asian concepts of illness, but also dismissing all of the patient's beliefs. Asian patients often suspect that some alchemical mixture of race and culture is the motivating factor behind Western physicians' dismissal of their beliefs. They fear that attitudes of cultural superiority and biological difference lurk beneath the surface. This underlying racial tension disguises itself as the patients' belief that different theories of illness are actually reflected in different disease mechanisms. The verbal expression of that racial tension as cultural superiority by Asian patients only leads to further frustration on the part of the physician. The readiness of many physicians to dismiss traditional Asian concepts of health only fuels this flame. Once the Asian patient rejects the applicability of Western medicine to his condition, compliance with physician recommendations becomes improbable. With a strong tradition to fall back on, the Asian patient may not feel that he is at any disadvantage in terms of receiving proper health care when he instead turns to alternative therapies of questionable value. It is left to the physician to wonder exactly why his efforts to provide care for the Asian patient are inadequate.

An exacerbating factor in Asian patients' often dissatisfying experiences with Western health care is a problem common to all immigrant populations: the language barrier. The inability of the physician and the patient to communicate properly often serves to reinforce the feeling on the patient's part that the physician does not really have any understanding of the illness afflicting the patient. The Asian patient becomes reticent, and often is embarrassed by the inability to communicate. My colleagues have interpreted the patient's silence as open hostility. They are, after all, accustomed to the normal banter between a professional and her patient. It is extremely difficult for the physician to sympathetically care for a patient in this context of silence. This scenario necessarily has negative implications for the quality of care and the patient's willingness to accept care.

The language barrier that magnifies the Asian patient's culturally based distrust of Western medicine is not solely the patient's fault. The physician who encounters a patient with whom he will have language difficulties cannot help but begin to feel less certain of the patient's history and physical examination. Often the physician will begin to simplify his speech in order to glean what he considers to be vital information. This is not necessarily a bad response to an uncertain situation; I myself have done the same thing when encountering Spanish-speaking patients. The simplification of communication, however, has specific implications in the treatment of the Asian patient. If the Asian patient distrusts Western medicine because it does not accord with his accustomed view of disease processes, then the physician's simplification of communication will only further alienate the Asian patient. The lack of an adequate explanation of the Western physician's rationale for treatment tends to reinforce the Asian patient's distrust. Without it, he lacks a clear rationale for treatment and has no reason to give the Western physician any credence, much less a reason to abandon his more familiar traditional notions of illness and health. The physician who is uncomfortable with the Asian patient and does not accord him an explanation reinforces the Asian patient's belief that the Westerner does not understand his illness.

At first glance, it seems that there is little that the private physician can do to counter the long legacy of culture and history. Actually, the methods that one can use to overcome the inherent distrust of some Asian patients are quite simple. We must keep in mind that many patients may not distrust Western physicians at all. For those who do, much of the distrust is present only upon initial encounters with a Western physician, and for the vast majority of these patients feelings of mistrust arise only in response to a perceived slight. The physician who is cognizant of the possibility of causing offense has many weapons in his arsenal with which to preempt misunderstanding and distrust.

The first point is to communicate acceptance of the Asian patient's traditional beliefs. The physician does not have to change everything the patient believes about health and illness; he just has to convince her that she should trust the physician enough to follow his advice. I have found it very useful to tell the patient that herbal medications work for some people, but not all patients, while the treatment I recommend has been shown to be the most effective in most people. So long as the patient understands that the physician is sincere and respectful, he will usually abandon his distrustful attitude.

The second point to keep in mind when dealing with a potentially distrustful Asian patient is to explain one's rationale. The great exacerbating element in distrust is ignorance. If the physician takes the time to explain the rationale for treatment, giving a traditionally minded Asian patient a reason to accept treatment, the patient will usually trust the physician. If given a good reason, most Asian patients will gladly follow the advice of the physician to the letter. Often, I have found that Asian patients will not understand exactly what I have said, but that my sincere effort to give an explanation will sway their decision away from traditional remedies and toward adherence with Western medical regimens.

Lastly, certain characteristics of Asian society lend themselves to overcoming any lingering distrust. Such small gestures as a simple greeting in the patients' native language, or the effort to pronounce the patient's name correctly, will often endear the physician to the patient and demonstrate the physician's respect for his person and his culture. Understanding kinship relationships at the core of Asian societies may also be worthwhile for physicians treating significant Asian populations. The physician's ability to function within those hierarchies will make the patient's attitude less adversarial. The whole point is to avoid the problem of the patient thinking of the physician as a threatening "foreigner" and to encourage the patient to view the physician as someone who is trustworthy and who will try to understand their native culture. This may be difficult for those with no experience with traditional Asian social structures or who only occasionally encounter Asian patients. Nevertheless, awareness of the nature of kinship relations allows the physician to recruit assistance from family and even friends of the particularly guarded Asian patient. If the physician can explain the necessity of compliance to an English-speaking close friend of a suspicious patient, she can be fairly certain of having a powerful advocate for compliance.

These statements are, of course, broad generalizations based on anecdotes and experiences, through the limited lens of one person's work with Asian patients and family members. I do believe, however, that they provide a useful framework for improving interaction with Asian patients. The fortunate fact is that Asian patients, though capable of suspicion, will usually accept care, and comply carefully with medical advice if given reasons to do so. In this sense, they are like most other patients. Asian patients are, in fact, more trusting than many African American patients, who unfortunately have historical justifications of their distrust of the medical profession. With an awareness of potential pitfalls, the physician can easily avoid the distrust of the Asian patient.

On Establishing Trust

Christine Kajubi

Abstract

Mutual understanding and trust are most easily attained between persons who share a common cultural background. Persons of color often see physicians as members of an alien culture who are not to be trusted. Physicians can and should transcend cultural barriers and secure the trust of patients of color. To do this, a common culture is not required; effort, kindness and sympathy are. **Key Words:** Medical ethics, physician-patient relationship, physician communication, minorities, health care.

No one here would protest too vehemently, I believe, if I were to say that it is easier to trust the familiar than the unfamiliar. It is apparent, for instance, that African people are most comfortable with other African people or that Eastern Europeans are more comfortable with other Eastern Europeans. It is also apparent that communication between Africans flows easily and that misunderstandings between them are relatively few. In the same vein, only an Indian person among other Indians can comfortably tell Indian jokes, only Jewish people can tell Jewish jokes, only camels can tell hump jokes. Certainly, a buzzard who tells hump jokes would get a cool reception from any self-respecting camel.

What needs to be involved in the interaction between a comic and his audience so that laughter results? Well, in order for a joke to be funny both the jokester and the listener must be operating within the same context. For example, "knock-knock" jokes are distinctly American. An American comic who makes his debut in Africa telling "knock-knock" jokes can most probably kiss his career goodbye. That the listener and his audience share a common language is also essential. After all, how can one who doesn't speak German laugh at a joke told in German? If a familiar context and a common language are present, then trust can follow. In particular, the listener can trust that the joke is not on her.

The relationship between a good physician and her patient is very similar to that between a comic and his audience. Permit me for a moment to return to our buzzard sitting comfortably in a tree telling hump jokes to a bunch of camels who are stiffly unamused. If this buzzard were to prove, by leading said camels to an oasis, that his agenda does not include hovering above them in anticipation of camel kebab, mightn't the camels loosen up? They might not find his jokes any funnier, but they just might trust, at least, that the buzzard means them no harm.

Now there may be some among you who believe that I have disgressed. So let me pause here to tell you that the buzzard represents physicians today and the camels represent those of their patients who are people of color. Unfortunately, there is little chance of running into Black or Hispanic physicians. People of color, for the most part, deal with physicians who not only operate within a different context but who also speak an unfamiliar language. If my discussion has made sense so far, it would follow that there is little chance for trust in this particular relationship. Can't a way be found to smooth over the differences?

Imagine for a minute that after a hard day at work you return home to find any one of the following scenarios: (1) your teenage son has bought you dinner with his weekly allowance; (2) your husband has brought you a single yellow rose on a day that doesn't even remotely resemble Valentine's Day; (3) your mother-in-law, hearing that you are recovering from the flu, has decided for your sake not to join the family for dinner after all. Unexpected events such as these can work wonders for one's mood. They might even make your day.

Now, think how you would feel if you were a patient whose physician has just approached you with a warm smile. Who doesn't understand a smile? Smiles don't need translation; they transcend the barriers of language. A smile can even make a person's day. Which mother's son wouldn't like to see his mother's medicine regimen written out on a small piece of paper so that his mother might refer to it daily? Doctors and patients don't have to speak the same language or even operate within the same context. They just have to establish a basis for trust, and the rest follows. Kindness, patience, and sympathy are universally comprehensible. Each of these can bridge barriers. They require only a modicum of effort. But why should you take this from me? After all, I am only a young medical student who tells buzzard jokes, and bad ones at that. Why take it from me? Simple. You must remember that although I am studying to be a buzzard, I was born a camel.

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The Hispanic, Gay, Lesbian, Bisexual and HIV-Infected Experience in Health Care

Milton L. Wainberg, M.D.

Abstract

This presentation, relying both on personal experience and an array of studies, surveys the problems minorities face in trying to obtain adequate health care. From another viewpoint, these are problems that physicians have in trying to provide health care to persons they do not understand and cannot really see or hear. And the problems multiply when the patient is a minority in more than one sense. The gay, Hispanic, HIV+ patient, for example, is removed from the average physician's comprehension to a degree that is itself almost incomprehensible. Treating patients as they ought to be treated requires that physicians overcome many layers of prejudice and unfounded assumptions. Failure to overcome such prejudices distorts medical practice. **Key Words:** Gay, lesbian, homosexuality, homophobia, racism, Hispanic, health care access, psychiatric population.

I HAVE THE TASK OF PRESENTING AN OVERVIEW of some of the difficulties that Hispanics, HIV-positive individuals, and gay, lesbian, and bisexual people experience in accessing health care. I am glad that others are presenting on the Hispanic experience. I shall also make some remarks about the severely mentally ill population, another minority with difficulty accessing health care.

I will report on statistics and research, and also try to bring my personal experience to this meeting. I guess the fact that I am gay and Latino, and that I work with people who have HIV and with the psychiatric population makes me a perfect guest speaker.

I shall discuss each of these groups separately. Yet, as you can imagine, any individual who belongs to more than one of them may experience difficulties exponentially greater than those which face members of only one of these minorities.

During my training here at Mount Sinai and at the Bronx Veteran Administration, which included rotations in psychiatry, medicine and neurology, I was impressed by some remarks made by a few of the attendings and my colleagues about these minorities and several others. As my Jewish last name does not reflect my Hispanic heritage, and not everybody with whom I trained was aware of my homosexuality, other health care providers did not monitor their comments in my presence. The prejudices I encountered are not unique, of course, to my experience. They are endemic and they reveal an important problem in our society.

Here is an anecdote which illustrates the problem. In my first year of training, during morning rounds, a prominent white male physician was telling us that Hispanic women are not very reliable patients, since one can elicit any symptom from them. He said something to the effect that "They are so histrionic and somatize so much that they will say yes to anything you ask

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them." To demonstrate, he conducted an interview and physical examination on a delightful 50-year-old Spanish-speaking woman. The woman was confused, yet respectful of this physician, who basically seduced her into agreeing with every manipulative question he asked. She never embarrassed him by letting him know that his Spanish at times did not make sense, that often she did not understand what he meant and only agreed with him out of respect, the way her culture expects her to. He felt he had proven the character of the Hispanic female patient. I am sure you can understand my rage at that moment. With the support of my chief resident, who also was enraged, I challenged his theory and reproduced the same interview and results with a middle-aged white woman just across the room. Needless to say, my evaluation in that rotation was the worst of my training. But what is worse, I feel embarrassed for my behavior for two reasons. As a lesbian colleague of mine pointed out, it might have been a better idea to choose a white man and not a woman for the second interview, so as to challenge his hypothesis about gender. Better yet, I should have repeated the evaluation with the Hispanic woman appropriately and, thus, demonstrated how to perform a thorough yet respectful interview. I should not have exposed another person to the same manipulation and humiliation.

So, what is the point of this story? The first thing, of course, is that this attending was unable to conduct a thorough and accurate evaluation because of his attitude. More important, all health care providers need to be aware of how our labels, preconceptions, fears and beliefs can interfere with our work.

Where do such labels, preconceptions, fears, and beliefs come from? Several factors may be involved. A terrible personal experience in our past may make it hard for us to deal with someone who reminds us of that experience. Also, in many different ways we are taught to fear, hate, or condemn some groups. We learn these attitudes from our parents, friends, schools, the media, movies, etc. And then there are idiosyncratic reactions to particular groups. Homophobia and racism can be an expression of our own internal difficulties. Some of the worst anti-Semites are closeted Jews. The same phenomenon occurs with individuals who fear homosexuality out of their own feelings for the same sex. One study of a group of self-defined heterosexual men who were exposed to gay male pornographic material reported that those subjects who had the worst regard for homosexuals or who showed a high degree of homophobia actually experienced penile erections in response to the materials (1).

Some people, even though versed in the realities of HIV transmission, fear contagion. The fear of contagion can be an unconscious fear. I have supervised many psychotherapy sessions and interviews of HIV positive individuals by medical residents where there was absolutely no possibility of physical contact with the individual and thus no possibility of contagion. Yet, such fears were evident in the behavior of the health care provider. At times, psychiatric patients also bring out fear in providers.

So, what are the repercussions on minorities of these labeling behaviors? Let me offer some relevant data. In the *Journal of Nursing Scholarship* in 1988, Stevens and Hall (2) reported the following about a sample of lesbians interviewed in the state of Michigan:

- 84% were reluctant to seek health care due to homophobia
- 40% feared they would receive inferior care if they "came out" or disclosed their homosexuality
- 84% found practitioners nonempathic
- 72% had experienced ostracism
- 96% of respondents indicated that they would get poorer care if their lesbianism were known.

In a 1989 survey published in the *Journal of Nursing Education*, Randall (3) found the following among the nursing faculty of a prominent school:

- 17% felt lesbianism is a disease
- 23% believed that it was immoral
- 34% claimed that it was disgusting
- 52% claimed it was unnatural
- 17% thought that lesbians molest children
- 8% felt that lesbians were not fit to be nurses.

In the 1987 *Journal of Medical Education*, Kelly (4) reported a survey of 119 Mississippi medical students. It revealed that gay men with AIDS or leukemia:

- Were seen as more responsible for their illness
- Were seen as being more dangerous to others
- Were thought to be suffering less pain than others
- Were considered and treated as inferior to heterosexual patients
- Were thought to deserve to lose their jobs, be quarantined, and die.

We could say that New York is different from Mississippi or Michigan. But a survey of third-year New York medical students published in *Psychosomatics* in 1990 by McGrory et al. (5) reported that students felt that:

- Patients with HIV were more responsible for their illness
- More than a quarter of their peers and half of their faculty had negative attitudes toward gay/lesbian patients and patients with HIV.

These attitudes explain the high rate of discrimination against gay, lesbian and bisexual professionals in the field of medicine. The currently utilized term "gay bowel syndrome" as a diagnosis is an insulting expression. Imagine a syndrome being called the "heterosexual vaginal syndrome" or the "straight male penis syndrome."

HIV/AIDS affects many minorities openly stigmatized or hated:

- Ethnic minorities—African Americans, Asian Americans, and Hispanics, where racism may have a big impact on their care

- Gays, lesbians and bisexuals, who may receive inadequate care because of homophobia and biphobia

- Intravenous drug (IVD) users, who also confront discrimination in their care.

Also, because of stigma surrounding the disease itself, many individuals with HIV/AIDS do not disclose their status to relatives and friends. Thus, relatives and friends may not be included in the provision of care, to enhance comfort and support. The HIV/AIDS epidemic intensely reflects the issues of access and allocation of health care. Unfortunately, HIV mostly affects stigmatized minorities. Many believe this is the reason that little has been done to help those afflicted by HIV, and to prevent the spread of HIV within minority communities. Perhaps those outside these minority communities think that it will stay within these populations. However, HIV does not discriminate.

In the 1970s and early 1980s, the "gay liberation" era, gay men were unknowingly infecting one another with HIV. Given their strong sense of community, their education and affluence, the white gay male community, even though heavily stigmatized, united to transform the economics, access and delivery of health care, as well as the speed of research implementation, approval and application. Community-based organizations like Gay Men's Health Crisis (GMHC), and Aids Coalition to Unleash Power (ACT UP) were the vortex of such activity. Unfortunately, it took several years before other minorities were included in this process.

Because of distrust of the medical establishment, many minorities do not seek treatment for their HIV-related conditions. You may have seen reports in the news that African Americans and Hispanics are benefitting less than Caucasians from treatments for HIV-related illnesses. However, with the development of the protease inhibitors, which can offer a new lease on life for some, there has been some influx of individuals from minority groups coming to our clinics asking for help and hope. Nonetheless, it is staggering to find out how many HIV-infected individuals are not getting care. Although HIV-related hospital admissions have decreased in number, homeless minority individuals who are not medically followed anywhere continue to have a high rate of admissions. Also, it has been my experience that, while they are hospitalized, HIV-infected individuals who require consultation from providers other than the HIV clinic's staff experience discrimination, delayed evaluations and, at times, refusal of indicated procedures and care. Providers in HIV centers spend many hours trying to get some consultants to do their jobs and trying to ensure that proper and nondiscriminatory recommendation are observed. Perhaps the substandard care may be explained by some of the data above about the attitudes toward homosexuals and IV drug users. The reality is that nobody wants or deserves to be infected with HIV.

Only recently have hospitals made some efforts to hire minorities. Just count how many minority physicians you know. You also do not see many openly gay, lesbian and bisexual physicians outside of HIV centers, where (perhaps) the attitude is to let gay physicians treat their own people. In general, the medical community is not inclined toward openness. Many gay providers will get only gay referrals, and not necessarily by choice.

Severely mentally ill individuals are also heavily stigmatized. On a unit for schizophrenic patients, one of my patients presented all the signs and symptoms of appendicitis. Yet the consulting surgeon believed the patient's delusions were influencing the clinical presentation and decided to wait. The surgical procedure performed the following day was much more complicated and dangerous than it would have been if performed earlier. As a consultant for psychiatric patients on medical floors, I often encounter health care providers who resist seeing the person behind the psychiatric diagnosis. Organic problems are often misdiagnosed as psychiatric symptomatology, and the risk of HIV infection is not associated with mentally ill individuals. As if psychiatric patients do not have sex or share needles! Researchers were surprised to find out that the rate of infection in the psychiatric population was similar to that in the rest of the population.

Let me give you some examples of the consequences of health care providers' attitudes.

Robertson and Schachter (6) reported in a 1981 survey that the interval between Papanicolaou smears was 21 months for lesbians, but only 8 months for heterosexual women, with the consequence of 2.7% of cervical dysplasia found in the lesbians screened. They also reported that the number of single lesbian women who had never been offered mammography is much higher than that of married or divorced women (6).

Research on teen suicide reveals that the rate of attempted and successful suicide is greater in gay teens. This research has also shown that suicide attempts often occur 24 – 72 hours after a visit to a health care provider (7 – 10).

Minorities do not trust the health care system. Thus, they often do not seek help until an emergency occurs. The reports of the Tuskegee study, of African American men with syphilis, substantiate minority distrust of the health care system.

As health care providers, we are in this business because we care about people, that is, all people, not just those who speak our language, share our sexual orientation, or share our heritage or our belief. We need to be aware that all of us carry some hatred in different degrees, so that we can transcend it and treat people appropriately. People must be made to feel comfortable and welcome to encourage their participation in their care. Do not allow fear of mental illness to affect your judgement. Respect the person's heritage, and understand and even enjoy their culture without judging or comparing it. Do not assume you know your patient's sexual orientation. Do not ask about your patient's husband/wife but about the person in his/her life, and ask their gender. If you learn that the patient's significant other is of the same gender, do not assume any stereotypes. And do not judge people by their illness. If you maintain the usual and appropriate precautions to decrease possibilities of contagion, you do not have much to fear. Listen to what the patient says. Do not fear that you will have to approve their behavior or do anything besides what you know how to do. That is why they have come to see you. If you don't know something, ask. If you do not know how to manage some problem, say that you don't and, as with any other question, consult for an answer.

Most important, remember that phobias and hatred are health hazards, and that we all carry hatred. Your professional goal is to create a comfortable setting in which to prevent, care for, or palliate illness. Do not let your hatred complicate illness.

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Patients' Rights and Professional Responsibilities:

The Moral Case for Cultural Competence

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Abstract

A right to health care can be derived from basic ethical principles. The empirical evidence revealing significant racial inequities in health status, access to health services, quality of care received and outcomes of health services is reviewed. The need for health care providers to acquire cultural competence in order to fulfill their professional responsibilities is discussed; the insight, knowledge and discipline required to function effectively in the context of cultural differences are described. The broader implications of cultural competence for institutional and public policy, research and professional education are outlined. **Key Words:** Ethics, cultural competence, minority health, physician-patient interaction, physician duties and responsibilities, outcomes, medical effectiveness, patient rights.

TWO AND A HALF DECADES AGO, when I was beginning my medical education, there was a popular slogan: "Health care is a right, not a privilege." This assertion has been, to a large extent, accepted into our collective view. Yet a sizable segment of our population still does not receive health care. I have spent the intervening years as an emergency physician. An emergency department provides an interesting perspective from which to view the health care system. Emergency care is the only type of health care to which access is guaranteed by law in this country. It is, therefore, inevitable that in the emergency department we see the failures of the health care system; we see the results of not having health care available to all. For vulnerable and disenfranchised populations, the emergency department is the health care provider of last resort, the safety net for a system which for many does not work well.

A Right to Health Care

Perhaps because I am so often directly faced with those who have been denied health care, I often reflect on this idea of a "right to health care." It is not difficult to derive the right to health care from basic ethical principles. Both teleological and deontological arguments for such a right can be made. Deontologists can argue that health is necessary to an individual's availing himself of any moral rights. Utilitarians might assert that, since the preservation or restoration of health is essential to an individual's ability to experience good of any kind, ensuring health care for each individual will result in the greatest balance of good over evil. It follows that depriving a person of the care required to restore or maintain health is unjust.

Severe threats to health can endanger life. So abhorrent have we found the withholding of care in such extreme cases that we have legally mandated the right to emergency care, regardless of an individual's ability to pay (1, 2). Furthermore, we have imposed a legal duty to provide emergency care upon both individual and institutional providers. However, we have limited this duty of providers to situations where care is believed to be necessary to protect persons from immediate threats to life or limb. This limitation would seem to have no basis in either ethical principles or fiscal prudence. Nevertheless, it is the current law of the land.

It is not my purpose here to engage in a debate about whether we as a society can or should provide health care to everyone. Surely we can agree that, as a commodity to which every individual can make a moral claim, whatever health care is available should be equitably distributed among the population. Equitable distribution, in the moral sense, requires the similar treatment of similars (3). For purposes of distributive justice, it is necessary to take a nonmeritarian view; we have a prima facie duty to treat people equally. Equal treatment does not mean identical treatment, but rather that the relative contribution made to the goodness of each indi-

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vidual's life should be the same. Help should be provided according to need (4).

It is morally wrong to deny any individual health care. It is unjust to systematically deny it to certain groups of people. Denial of health care on the basis of race might be regarded as particularly repugnant in a society which has outlawed *de jure* racial segregation. However, there is no doubt that this is the situation in America today.

Minorities, Health and Racism

Philosophers from Socrates onward have emphasized the value of factual accuracy and conceptual clarity as precursors to moral deliberation and ethical reasoning (4). The current situation of racial minorities with respect to health and health care is not a matter for ethical debate, it is a matter of empirical fact. A rigorous examination of the available data leads inescapably to the conclusion that significant racial inequities currently exist with respect to health in this country (5–7).

The need for health care is unequally distributed in the population. The poor health status of certain racial groups is well documented both by population-based data and numerous cohort studies (8–11). Disease-specific indices demonstrate greater mortality and morbidity among certain racial groups for heart disease and hypertension (12–16), asthma (17, 18), end-stage renal disease (20), diabetes (21), cancer (22, 23), low birth weight and infant mortality (24–26), and HIV/AIDS (27–29). African Americans, Latinos and Native Americans have demonstrably poorer health status than white Americans (30–32).

Furthermore, these same racial groups have unequal access to health care. Financial barriers, logistical barriers, cultural, linguistic, organizational, institutional and systemic barriers disproportionately affect African Americans, Latinos and Native Americans (33–36). Not only is access to health care for these racial groups unequal, but much of the evidence suggests that the gap is widening (37, 38). And for minorities who are successful in accessing health care services, (according to a growing number of studies), the quality of the care received is unequal to that received by whites (39–41). It is true that the measures of quality currently available are imperfect. However, it is likely that the measures are biased in a way that minimizes the difference between groups. Even so, they clearly indicate disparities in the quality of care received.

Medical effectiveness research is a new conceptual and methodological field of inquiry which examines the patient outcomes associated with clinical interventions (42). Although population-specific effectiveness research is in its infancy, the extant data reveal racial differences in outcomes, even when intermediate and contextual variables such as access, utilization, provider profiles and socioeconomic patient characteristics are taken into account (43–45).

It is worth mentioning that there are serious methodologic issues which complicate the interpretation of much of the data currently available on racial differences in health status, access, quality and outcomes (46–48). It has been convincingly argued that race is not useful as a biologic taxonomy; intra-racial genetic variation exceeds interracial variation (49, 50). It is most useful to think of race as a complex amalgam of biological, psychological, sociological and environmental factors (51, 52).

One frequently encounters the assertion that minority groups' differences in health can be explained by differences in socioeconomic status. Although many find economic discrimination more palatable, it seems to me that socioeconomic status is no more morally relevant than is race as a criterion for differential health care treatment. In any case, the assertion is incorrect: race is not a proxy for socioeconomic status. Studies reaching such a conclusion are invariably flawed in their sampling, their measures of socioeconomic status or their interpretation of the data.

There is, in America, a statistical correlation between race and the three components of socioeconomic status: education, occupation and income; there are also interactive effects of race and socioeconomic status on health (53–55). Without elaborating upon the complex relationship between socioeconomic status and race, it is fair to summarize the existing literature in this way: when socioeconomic status is adequately measured and controlled for, racial differences in health status, access, quality and outcomes persist. The most compelling models for explaining these racial differences in health among African Americans, Latinos and Native Americans hypothesize that racism, both individual and institutional, plays a role in creating these differences (56–58).

I submit that racial minorities have been and continue to be wronged by the American health care system. I believe that we, as members of this society, have an obligation to correct this injustice and that health care professionals have an even greater obligation. As comfortable as it may be to attribute this wrong to "the system," the system and the institutions that comprise it are ultimately the creation and the result of individual actions. We must assume that, knowingly or unknowingly, health care professionals have contributed to current racial inequalities in health and health care.

Responsibilities of Health Professionals

What, then, are the responsibilities of health care professionals with respect to racial minorities? The duty of a health care provider to any patient includes several elements. The first is competence. We have a duty to acquire and maintain the skills and knowledge necessary to provide care to our patients. The second element of our professional duty to patients is respect. We must show respect for patients' autonomy and for the values and beliefs upon which they base their choices and decisions. The third important element is the duty to be beneficent, to have compassion for each patient with whom we establish a professional relationship and to act in that patient's interest, rather than our own.

These professional responsibilities are recognized by every statement of professional ethics from the Hippocratic Oath to the current policy of the American Medical Association. These professional responsibilities carry the weight of moral duty. Clearly, health care professionals have an obligation to provide competent, respectful and compassionate care to all of their patients, including those who are members of races other than their own.

I believe that achieving this goal involves the acquisition of cultural competence, that is, the ability to function effectively in the context of cultural differences. Development of cultural competence begins with an honest and insightful inquiry into one's own feelings, beliefs and values in order to detect internalized attitudes which may disadvantage certain patients. Cultural competence requires sufficient professionalism to ensure that culturally, racially or ethnically biased attitudes do not affect the care rendered to patients. Cultural competence also requires knowledge. Health care providers must have a knowledge of ethnic and racial differences in health-related beliefs and cultural values, of ethnic and racial differences in disease incidence and prevalence, and of ethnic and racial differences in treatment efficacy. Cultural competence demands an awareness of the effect of race on these issues and integration of that awareness into one's communication with and treatment of patients (59, 60).

It is our responsibility as professionals to provide effective, respectful and compassionate care to every individual. It is our duty to overcome whatever obstacles threaten to prevent our delivering of such care (61), whether the obstacles are based on racial differences or personal idiosyncrasies. We must have sufficient knowledge to correctly identify the patient's needs and we must appropriately apply our generalized knowledge to the specific situation. We must be skillful communicators, good listeners and astute observers. We must respect each individual and we must be flexible enough to gain the cooperation and participation of our patient.

Experienced clinicians may recognize that the traits required to achieve cultural competence are the same traits used to engender trust and satisfaction in any provider-patient encounter. It is also interesting to note that arguments for cultural competence are not limited to ethical ones; one can make persuasive arguments that the effectiveness of care and the financial success of the provider or institution are enhanced by culturally competent practitioners (60).

The current racial inequities in health offer health care professionals ethical challenges beyond the physician-patient encounter. We must work to change institutional and public policies which result in the perpetuation of race-based inequities in health. We must address these inequities through our research and develop strategies to improve the health status and health care of racial minorities. We must ensure that our professional education programs produce practitioners with the skills and knowledge they will need to serve an increasingly diverse population. On every level, we must work to eliminate the inequities in health status, access, quality and outcome among the different races, which currently characterize our society.

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Stop Experimenting on My Baby!

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Abstract

Having a small sick baby in a neonatal intensive care unit can be an extremely difficult experience for any family. A minority family brings to this setting the additional burden of a concern that racism may affect the care their child receives. While the technology may be overwhelming, the unique rules and an apparent disparity in the enforcement of these rules can suggest discrimination. In some cases, these parental perceptions lead to a charge of experimentation. An increased understanding by health care providers of the cultural differences and life experiences that families bring to stressful situations can improve communication. **Key Words:** Bioethics, neonatology, minorities.

I WOULD LIKE TO RELATE SOME OF THE ISSUES that I, as a neonatologist, encounter when dealing with some of the families who have small, sick neonates in the intensive care unit. I want to preface this discussion by acknowledging that having a critically ill child can bring out both the best and the worst in people. I say this knowing that it often takes marked restraint not to become angry when a parent launches into a thinly veiled personal attack.

Let me start by sketching the setting. The neonatal intensive care unit (NICU) is large, busy and, unfortunately, rather noisy. Thirty to forty babies are in various states of health. Most live in incubators, attached to monitors for heart rate, breathing, oxygenation, and temperature. They have intravenous catheters in veins and plastic tubes in blood vessels in the umbilicus. Gastric tubes are coming out of their noses, and a number of the babies are attached to respirators. Alarms go off every few minutes. Imagine yourself as a 17-year-old African American mother who delivered a two-pound baby girl—your first pregnancy. You are in your last year of high school and your boyfriend, the father of the baby, hasn't been all that interested in you since you got pregnant. Although you did go to some of your prenatal visits, others were at times that interfered with school or being with your friends. Labor and delivery were scary and painful, and you delivered your daughter in an operating room filled with doctors, nurses and machines. You barely saw your baby at her birth, and a group of people with masks and caps took her away after hovering over her for what seemed an eternity, right after her birth.

With this introduction to neonatal intensive care, this mother must try to understand who we are and what we do. But why is this an issue unique to minorities? Surely, white Upper East Side investment bankers don't come with a prior knowledge of neonatal intensive care. What they do come with is an implicit trust in medical technology and in our ability to heal. For those families, any failure implies we didn't do everything we could. We weren't smart enough, skilled enough, computerized enough, technical enough. For our young African American mother, at issue is not our abilities but our motivation. That's not to say that we won't be questioned about our skills or that our young mother won't realize that various doctors and nurses have varying capabilities. It's just that there is a more significant problem that we must always keep in our minds. Our young mother does not believe that my primary goal is to care for her little daughter with all my heart and soul.

What do we do to make her mistrust us? Is it the overwhelming technology that comes between us? We assume it's comforting to see our high-tech response to a two-pound baby, but in fact,

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our mastery of this technology makes our young mother feel frighteningly powerless. Every parent of a sick baby feels powerless. We know this and we help parents verbalize this feeling. However, this is more difficult with our young mother, who is not willing to discuss her feelings with me. I don't blame her. She certainly doesn't know me, and there is obviously a long history of inequality and racism that clearly places our ability to communicate openly in question. For most families, their lack of power doesn't immediately translate into an adversarial relationship with the health care provider. It is more often an emotional response to the "bad luck" of their being in such a situation. The young African American mother, however, sees me as part of a technology not to be trusted. I am not only powerful but "different." As in any situation of unequal power, it is not unusual to examine motives.

Not only do we overwhelm her with our technology, but the NICU is a place with rules that are different from those at home. We demand strict adherence to the limits we place on visiting hours, the number of visitors, the noise level, etc. And then we appear to enforce these rules unequally. We are much less likely to ask the extended family of the Upper East Side investment banker to leave than the lively young cousins of our 17-year-old mother. Our young mother sees that I might spend 10 – 15 minutes speaking with the family of the investment banker and only a couple of minutes with her. It doesn't matter that they engaged me in a long discussion of medical details and that she had little to say. From her perspective, I've chosen sides.

All of this leads to the title of this talk, "Stop Experimenting on My Baby." Over the last decade, I have been accused (as have many of my colleagues) on more than one occasion, of experimenting on an infant. The scenario is often similar— a baby has been very ill and in our unit for an extended period of time, and a small group of African American mothers, all with babies in the NICU, have become close friends. Each has had something happen to her baby which we, the health care team, have been unable to clearly explain or prevent. Maybe her baby had an intraventricular hemorrhage and developed hydrocephalus, or a patent ductus arteriousus failed to close spontaneously and heart surgery was required. A central intravenous catheter may have become infected with yeast and we are having difficulty finding sites for IVs, so we shaved a part of the baby's hair. Maybe we are keeping a baby alive on a respirator in a situation where discontinuing support is generally felt to be unethical. Needless to say, never have we "experimented" in the medical/technological sense.

In some of these cases, the accusations are not made directly but are overheard in the parent lounge by a passing staff member. In other cases, there is a direct and angry confrontation over this issue: How can I not see or believe that we are experimenting? I, as the master of this technology, can't answer this or other seemingly easy questions. Yet I have answers for everyone else. Other babies are getting better. Only the babies of African American mothers seem to have these kinds of problems. Any failure in this unfathomable and foreign NICU must be because I can't be trusted. It happened because I allowed it to happen. Are they right and am I wrong? The quick answer would be no, but that might not be totally true. There is an element of truth in the accusation and it certainly has solid historical roots. Remember the delivery of this tiny baby. We presented ourselves as "automatons" sweeping this baby off to the NICU, promising to apply our high-tech miracle cures. We tried to be compassionate, but that is so hard in the setting I've described. Sure, we hedged and gave numbers of survivors and all the rest, but we-the-system held out hope. However, a high-tech system is not infallible, so, not surprisingly, the time comes when we "cannot be trusted." As scientists and technocrats, when "things" don't go right, we must be doing something other than curing. To our young mother, experimentation is the obvious answer. To me, each patient is an "experiment" (but not in the layperson sense), whom I hope to cure with tools that don't always work. My motives are simple and sincere, but they become entwined with hundreds of years of painful history and experience. To my young mother, the same scenario, without trust, is also an experiment. But this experiment isn't working, and I shouldn't have done it to her baby.

Do I have a solution? Not exactly! I don't think we will be able to really gain the trust of our minority patients until it becomes clear to them that the medical system is designed fairly for all people. There is no use simply claiming that it is. In the interim, I believe that health care providers can diminish the likelihood of being accused of experimentation by recognizing the bases of that charge. It should not seem incomprehensible to each of us that patients don't trust our motives. Recognizing that fact will probably improve our ability to communicate and increase our sensitivity to important cultural differences and the generalized effects of discrimination.

'Tis Better to Receive than to Give:

The Relative Failure of the African American Community to Provide Organs for Transplantation

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Abstract

There is a serious, continuous and increasing shortfall of organs, especially kidneys, for the purpose of transplantation. This shortfall is especially remarkable in African American populations. Because the incidence of hypertension (HTN) and associated end-stage renal diseases (ESRD) is 17 times greater in African Americans, this minority group, which comprises only 12% of the U.S. population, represents 34% of the dialysis population and 30% of the national kidney waiting list. Furthermore, while black individuals comprise 22 – 24% of kidney recipients, they comprise only 8 – 11% of donors. Because of the histocompatibility differences between the races and because tissue matching is part of the United Network for Organ Sharing (UNOS) allocation formula, African Americans wait twice as long for kidneys as Caucasians. Also, because they get more poorly matched organs, their kidney transplant graft survival is 10 – 20% lower than that for other racial groups. The African American community is unaware of the special needs in members of their own race. Steps must be taken to increase minority awareness of the need for well-matched transplant organs and their involvement in the donation process. **Key Words:** Organ donation, kidney transplantation, organ transplantation, organ donation by minorities, organ shortage.

THE TRANSPLANTATION PROCESS is probably the most carefully administered medical program in our country. Virtually every aspect of procurement, allocation, and subsequent results of transplantation are monitored on an hourly basis and recorded in a national data bank.

Because of the remarkable advances in the field of transplantation, the majority of organ failure patients can now be offered a reasonable chance of a normal life. Accordingly, with more sick individuals opting for this therapy, the shortfall in donor organs is increasing. Thus, with the supply not keeping up with the demand, more patients are dying for lack of life-saving transplants.

The following two case histories help illustrate one puzzling reason for this shortfall.

Case 1. A 19-year-old respirator-dependent female, living at home after an auto accident two years before, suffers a respiratory arrest when a tracheostomy plugs and an alarm system malfunctions. She is declared brain dead and her family wills a single kidney only to a 60-year-old diabetic, hypertensive father who has been on dialysis for 8 months. No other organs are offered, but her liver is also donated when the procurement coordinator informs the family that the medical examiner will take it anyway. All the other potentially transplantable organs are wasted.

Case 2. A 35-year-old with heroin-induced nephropathy has been on dialysis for 5 years when his 55-year-old mother, a school secretary, suffers a fatal stroke. His family, which includes a sister who is a dialysis nurse, offers the mother's kidney only to him. No other organs are offered. When the family is informed that the patient is too infected at that time to undergo transplant surgery, they withdraw their offer of donation and this organ is also wasted.

One salient fact has been omitted from both of these histories. Both families were middle-class African American families. The African

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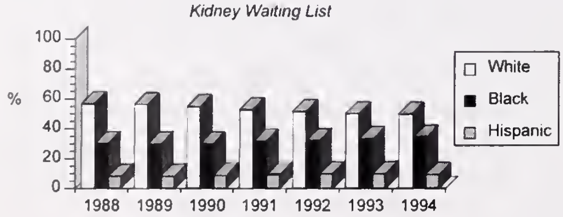
American community has been providing donor organs at a significantly lower rate than that of the white population (1, 2). This imbalance has been detrimental not only to the recipient population at large, but especially to African American patients waiting for transplants.

Why this disparity? Dr. Clive Calendar, a transplant surgeon and also an African American, has been seeking the reason(s) for this unwillingness to consider organ donation since the 1970s. He has spearheaded and participated in many minority research programs. In 1980, the results of one of these research efforts showed that the incidence of hypertension and associated renal disease was 17 times greater among African Americans than among Caucasians. Even though African Americans make up 12% of the national population, 34% of the dialysis patients in the U.S. are African American. Furthermore, of those waiting for kidney transplants in the U.S., 30% are also African American. Unfortunately, the kidney transplant graft survival for African Americans is 10–20% lower than for any other racial group. In addition, African Americans wait twice as long for kidneys as Caucasians, and their organ donation rate is less than 8% (3).

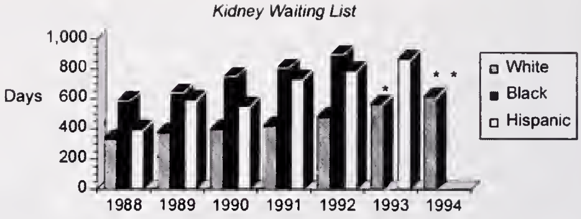
According to data from the United Network for Organ Sharing (UNOS), African Americans comprise 30–35% of the patients on the national waiting list (Fig. 1) (1). Yet they clearly wait longer than any other racial group (Fig. 2). One might wonder whether discrimination is a factor in this difference—but the UNOS allocation system for kidneys is strictly patient driven, without respect to race and—with the exception of children under the age of 17—without respect to age as well.

The United Network for Organ Sharing assigns points to each candidate waiting for a kidney, using specific standardized criteria (Table). These points include the duration the prospective recipient has been on the transplant list, and the degree of tissue typing (Human Leukocyte Antigens—HLA) match with the donor. For those patients who are immunologically very sensitized (as indicated by elevated Panel Reactive Antibodies—PRA), additional points are assigned, since it is very difficult to obtain a compatible organ for them. The point scores of each prospective recipient are then totaled and ranked by computer with every cadaver organ. The prospective recipient's placement on the UNOS printout depends on that total score. The poor antigen matching for African Americans is also reflected by the shortfall of black donors, and has been cited as one of the causes for their 10–20% lower kidney graft survival rate.



UNOS 1995 Annual Report

Fig. 1. Percentage of patients by race. Kidney waiting list. From the United Network for Organ Sharing (UNOS) 1995 Annual Report on U.S. Scientific Registry for Organ Transplantation & Procurement, Richmond, VA (1).



* cannot be determined, too few transplants

UNOS 1995 Annual Report

Fig. 2. Median waiting times to transplant. Kidney waiting list. From the United Network for Organ Sharing (UNOS) 1995 Annual Report on U.S. Scientific Registry for Organ Transplantation & Procurement, Richmond, VA (1).

The bar graph in Fig. 3 shows the percentage of patients transplanted for the years 1988–1994. When compared to the percentage of kidney donors by race as seen in Figs. 4 and 5, clearly the disparity between Caucasian, and African American and Hispanic recipients is shown. African Americans have historically donated significantly fewer cadaver kidneys than they have received. They have received and benefited from Caucasian organ donation (1).

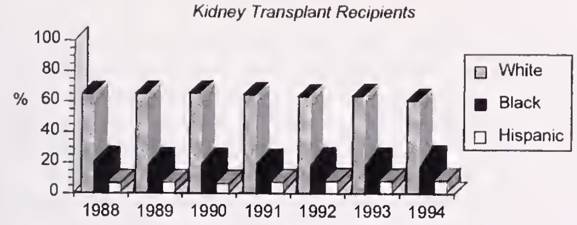
Since 1988, there has been a slight increase in the percent of total minority donations: from 16.4 to 22.8% for cadaveric donors and for living

TABLE

The UNOS Point System for Local Kidney Distribution.

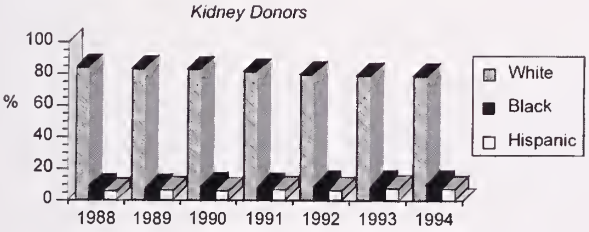
Points	Category
2–7	HLA matching
complex formula	Time waiting
4	PRA ≥ 80%
4	Age < 11 years
3	Age 11–18

From the United Network for Organ Sharing (UNOS) Policy 3.5. March 24, 1999 (4).



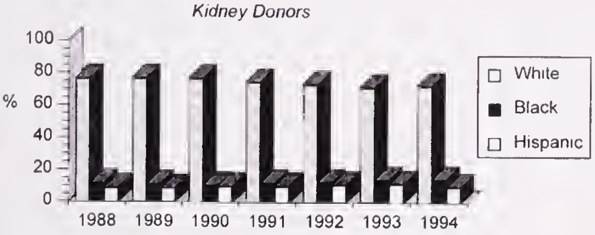
UNOS 1995 Annual Report

Fig. 3. Percentage of patients transplanted by race. Kidney transplant recipients. From the United Network for Organ Sharing (UNOS) 1995 Annual Report on U.S. Scientific Registry for Organ Transplantation & Procurement, Richmond, VA (1).



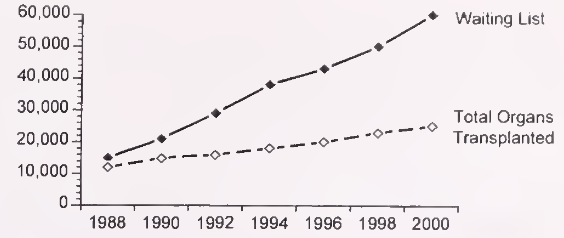
UNOS 1995 Annual Report

Fig. 4. Cadaveric donors by race. Kidney donors. From the United Network for Organ Sharing (UNOS) 1995 Annual Report on U.S. Scientific Registry for Organ Transplantation & Procurement, Richmond, VA (1).



UNOS 1995 Annual Report

Fig. 5. Living donors by race. Kidney donors. From the United Network for Organ Sharing (UNOS) 1995 Annual Report on U.S. Scientific Registry for Organ Transplantation & Procurement, Richmond, VA (1).



UNOS 1998 Update

Fig. 6. UNOS - wait list size and total organs transplanted. From the United Network for Organ Sharing (UNOS) 1995 Annual Report on U.S. Scientific Registry for Organ Transplantation & Procurement, Richmond, VA (1).

donors an increase from 24 to 27.5% (1). This fact, however, is overshadowed by the ever-increasing demand for organs (Fig. 6). Why then, in light of the special need for organs by African Americans, has there not been a similarly greater donation rate? Why do African Americans say no to donation?

Dr. Clive Calendar identified the obstacles to donation in the minority community as lack of awareness, fear of premature death, religious beliefs or concerns with issues of resurrection, and the belief that body parts would be needed in the other world. Another factor cited is the lack of trust that medical professionals would do everything possible to save their loved ones if the family was to consider organ donation. The history of the Tuskegee experiment serves to reinforce this mistrust. Some have even expressed the view that medical professionals work on a commission basis and would benefit from their loved one's death. Some African Americans consider the signing of a donor card as akin to a "death wish." Also, some African Americans bear hostility toward whites for the years of oppression and feel that they are owed something for it—yet here they are being asked to give away something of great personal importance (2).

What are the possible solutions to this problem? It has been recommended that minorities be included and involved in the planning and implementation of the donor process within their communities. This participation would allow them to be part of the solution to the donor shortage and would help empower their community. Another suggestion has been to utilize key persons from minority groups, such as transplant recipients, transplant donors, transplant candidates and donor families, as effective messengers to help overcome distrust of medical professionals. Also, the public and private sector should expand funding to pay for the cost of preparing and marketing materials such as videos and brochures, which would enhance donor education. And finally, steps need to be taken to foster positive media representation of the organ and tissue donation process (2).

In conclusion, African American patients receive a disproportionately larger number of transplant organs—especially kidneys—from the cadaver donor pool, but African Americans donate organs at a significantly lower rate. The withholding of organs by this community is detrimental to the African American dialysis population, which must wait much longer for organs than Caucasians and generally receive more poorly matched kidneys because of histocompatibility differences between the races.

The reluctance to donate may be due to mistrust of the medical establishment as well as to lack of awareness, to religious beliefs, to fear that signing a donor card could lead to withdrawal of needed medical treatment, and to resentment of past or present racism.

Without a doubt, if more African American families were involved in the donation process, all patients would benefit greatly. Concerted efforts must be made to educate and involve this segment of the population in the donation process.

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Blood Transfusion and the Pregnant Jehovah's Witness Patient:

Avoiding a Dilemma

David H. Schonholz, M.D.

Abstract

The pregnant Jehovah's Witness patient's refusal of lifesaving transfusion creates a conflict for the physician. While legal steps may be initiated to address the problem, a medical approach stressing prophylaxis which anticipates and avoids the ethical dilemma of managing a hemorrhaging pregnant Jehovah's Witness is preferable. **Key Words:** Jehovah's Witnesses, blood transfusions, pregnancy, management protocol.

For the most part, the birth of an infant is an occasion for joy. Complications, however, can be life threatening. Of these, hemorrhage is one of the leading causes of maternal mortality. The average pregnant woman usually has a blood volume of about 6 liters, so that any blood loss estimated to be 1500 mL or greater may be life threatening. When a pregnant patient continues to bleed, death may be inevitable. The therapeutic goal in the event of hemorrhage is to maintain normal tissue perfusion and stop active bleeding. In due time, under normal circumstances, compensatory mechanisms of increased red cell production will correct severe anemia (1).

All health care personnel who provide labor, delivery and gynecology services should be prepared to manage hemorrhage, because adequate preparation can save lives. Every effort should be made to identify patients with known risk factors for uterine atony (overdistended uterus from multiple pregnancy, prolonged labor, fetal macrosomia) or potential bleeding (high parity, uterine inversions, placental abnormalities, ectopic pregnancy, fibroid uterus, endometriosis). It is especially important to identify and prepare for patients who are Jehovah's Witnesses, because in the event of a complication, they will refuse to accept blood transfusions and most, if not all, blood products.

The Jehovah's Witness Society is a Christian sect based in Brooklyn, NY. Today, in the metropolitan New York area, the vast majority of Witnesses are African American or Hispanic. The mistrust of medicine common in these groups is compounded, in the case of Witnesses, by fears that doctors will not respect their religious beliefs, in particular their opposition to transfusion or the use of blood products.

The Witnesses' opposition to transfusion is based on their interpretation of the following scriptural passages from the New World Bible (1984):

> *Genesis 9:3–5 . . .*
>
> *Leviticus 17:13–14 . . .*
>
> *Acts of the Apostles 15:19–20 . . .*

Physicians tend to discount or underestimate the importance of the Witnesses' faith-based need to

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'abstain . . . from blood,' where it is taken to include the refusal of transfusion. From the Witnesses' point of view, however, blood transfusion has serious consequences: "excommunication . . . forfeiture of a chance for eternal life, and severance of the individual's relationship with God" (2). These are not the sorts of adverse outcome physicians usually have in mind when they assess a procedure's risks. If physicians dismiss such patients' most profound concerns, however, they put their relationships with their patients, and with the entire community of Jehovah's Witnesses, at risk.

The physician-patient relationship ought to be governed by the moral principles of autonomy and beneficence. Respect for patient autonomy requires that the physician allow the patient to live by her own values. This entails that it is her decision whether to accept or reject recommended treatment options. Beneficence obliges physicians to promote their patient's well being. These two principles clearly come into conflict in the case of the pregnant, hemorrhaging Jehovah's Witness patient who refuses lifesaving transfusion for reasons of faith (3).

Treatment approaches to such cases have, in large part, been determined by the law (4). Based on the doctrine of *parens patriae*, or the power of the state to preserve the lives of minors, the courts have ruled for the transfusion of minors (pregnant or not) in life-threatening situations (4, 5). Competent non-pregnant adults are allowed to refuse life-preserving transfusions, and physicians are not permitted to override their decisions. Cases where the fetus will perish because of the adult mother's refusal of blood transfusion remain the most ambiguous and troubling. Recent legal opinions on this issue differ. Some decisions hold that the mother's rights are supreme on the Constitutional grounds of freedom of religion, the right to privacy, and the right to act on one's own conception of the good by refusing medical care. These decisions conclude that the woman's choice should not be overridden (3). Other decisions focus on the irrevocable harm to the fetus which transfusion refusal may cause, the minimal risk to the mother which the procedure carries, and its likely efficacy. These decisions emphasize the importance of protecting fetal life and preventing the abandonment of minor children. They conclude in favor of overriding the woman's choice. Women in the second and third trimesters of pregnancy have actually had guardians appointed to permit transfusions for the fetus (4–8). Legal decisions reflect the variety of contemporary moral points of view, but regardless of the legal verdict in a particular case, resorting to the courts destroys the physician-patient relationship.

One practical and moral solution to the problem is to anticipate the potential need for transfusion and to have techniques in place for management of blood loss without transfusions, so as to obviate the need to violate autonomy, sacrifice beneficence or damage the physician-patient relationship (9). To that end, and to secure the trust of the Jehovah's Witness community, the Department of Obstetrics, Gynecology and Reproductive Medicine of the Mount Sinai Medical Center enlisted assistance to create a protocol based on the philosophy of prevention. Creation of the protocol (10) was the work of a committee with members from Mount Sinai's departments of Obstetrics, Gynecology and Reproductive Medicine, Anesthesia, Hematology and High-Risk Fetal Medicine, working with the Ethics Committee of the Medical Board, the Legal Department, the Federation of Jewish Philanthropies (FOJP) Malpractice Hospital Unit, and the Jehovah's Witness Society's Liaison Committee.

The protocol can be summarized as follows:

1. Require that all obstetricians who register or admit Jehovah's Witness patients attest that they understand relevant departmental protocols.

2. Obtain the patient's informed consent for anticipated or potential procedures by approximately the 28th week of the pregnancy, using the generic hospital consent form, the Watchtower Society Acknowledgment form (Health Care Proxy—NYSPHL #2980-2994) and the blood product check list form, which indicates which blood products the patient is willing to accept, if any.

3. Prepare medically by arranging for

    a. Anemia correction: if a patient's hematocrit is more than 40%, using iron and folic acid; if the patient has a hematocrit less than 40, then erythropoietin, which contains a blood-derived product but is acceptable to most Witnesses, may be indicated.

    b. Preoperative evaluation, including the potential use of interventional radiology, embolization catheter or vascular balloons.

    c. Anesthesia review, with prescheduling of cell-saver apparatus, use of plasma expanders, hypothermia and hyperdilution techniques.

d. Intraoperative use of cell saver with strict surgical techniques for hemostasis.

4. Consult with an attending in the division of Maternal Fetal Medicine, before 28 weeks and in all obstetrical emergencies.

By taking the Witnesses' needs seriously and conveying to Witness patients that their needs will be taken seriously, we can avoid becoming their adversaries. Instead, we are their partners.

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Appendix
New World Translation of the Holy Scriptures (1984)

(Genesis 9:3–5) Every moving animal that is alive may serve as food for you. As in the case of green vegetation, I do give it all to you. 4. Only flesh with its soul—its blood—you must not eat. 5. And, besides that, your blood of your souls shall I ask back. From the hand of every living creature shall I ask it back; and from the hand of man, from the hand of each one who is his brother, shall I ask back the soul of man.

(Leviticus 17:13–14) As for any man of the sons of Israel or some alien resident who is residing as an alien in your midst who in hunting catches a wild beast or a fowl that may be eaten, he must in that case pour its blood out and cover it with dust. 14. For the soul of every sort of flesh is its blood by the soul in it. Consequently I said to the sons of Israel: "You must not eat the blood of any sort of flesh, because the soul of every sort of flesh is its blood. Anyone eating it will be cut off."

(Acts 15:19–20) Hence my decision is not to trouble those from the nations who are turning to God, 20. ...but to write them to abstain from things polluted by idols and from fornication and from what is strangled and from blood.

African Americans and the Medical Establishment

CHERYL SMITH, M.D.

Abstract

The African American community's response to the AIDS epidemic has reflected the profound mistrust of the medical establishment which many African Americans feel. Among African Americans, the belief that the epidemic originated in a genocidal plot is widespread. It is thought that organized medicine has been significantly involved in this plot. If we look at African Americans' historical relationship to the medical establishment from the era of slavery to the recent past, the suspicious attitudes which make such beliefs possible can be seen as an intelligible response to a new disease which disproportionately affects African Americans.

Successful medical and public health responses to the epidemic have depended and will continue to depend upon overcoming the historical legacy of suspicion and gaining the trust of the community.

Key Words: African Americans, AIDS, history of medicine, medical ethics, Tuskegee Syphilis Study.

THE AIDS EPIDEMIC has taken a significant toll on the black community. Blacks make up 13% of the United States population, yet, they accounted for 57% of all AIDS cases in 1997. AIDS is the leading cause of death among black men and women aged 25 – 44. Blacks and Hispanics account for 84% of pediatric AIDS cases (1).

The initial reaction of the African American community to the AIDS epidemic was marked by overwhelming suspicion and fear. In discussions of the epidemic, the word "genocide" was broadcast on the airways of WLIB and appeared in print in the *Amsterdam News*, the *Los Angeles Sentinel, Essence, Ebony*, and *Jet*. Early in the AIDS epidemic, articles with such titles as "Natural Epidemic" (2) and "AIDS: Is It Genocide?" (3) were common. I quote from the second article by Bates (3):

> The time: the late 1970's. In a well-guarded laboratory complex in an American suburb, an elite conference of biologists, demographers and political scientists listen closely to the report of an epidemiologist. This physician, who studies the origins and progress of diseases, is telling the group that he has created a virus that will render the human immune system powerless. A simple cold that would leave a healthy person miserable will kill people who have been exposed to this virus. There is no cure. It is always, always fatal. "We can use this virus to eliminate certain populations," he explains. "We thought we'd try homosexuals first—nobody cares what happens to them, anyway, there'll be little outcry. And if the virus proves effective—we can move on to other populations. Like the Black underclass. That'll help cut down on the dollars you have to spend on welfare." The room chortles in agreement. The meeting is adjourned.
>
> A few years later, in San Francisco, New York, Miami and Los Angeles, gay men begin to sicken and die. A few years after that, poor Blacks also succumb to the same puzzling symptoms. The genocide project has begun.

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Discussion of the possibility that the epidemic has its origin in a genocidal plot was not limited to the lay community. The theory was embraced by some African American physicians. Dr. Barbara Justice, for example, is quoted as saying "There is a possibility that the virus was produced to limit the [number of] African people and people of color in the world" (3). Others, such as Dr. Greaves, sought to turn attention away from conspiracy theories. In his view, "it is dangerous to be preoccupied with theories [of an AIDS conspiracy] when we need to work on containing the disease" (3).

The opponents of conspiracy theories often spoke in scientific terms that were unfamiliar to the community. As a result, they were often ignored. Dr. Justice's comment, however, rang loudly to the many people in the African American community who had long feared and mistrusted the medical establishment.

The "pre-existing" fear and mistrust of the medical establishment has its roots in slavery. During the antebellum era, organized medicine contended that Africans had peculiar anatomic and physiologic features. These alleged differences were used to justify their enslavement and brutalization (4). In 1845 and 1849 Dr. Marion Sims, considered the father of modern gynecology, used three female slaves to develop techniques for the repair of vesico-vaginal fistulas. He did not use anesthetics. When these techniques were perfected, white volunteers were unwilling to undergo the painful procedures (5). Studies of various pharmaceutical agents were conducted to lengthen work hours on hot days in the fields (6). Countless other undocumented acts of medical abuse are recounted in the oral histories of the African American families. Fear of medical experimentation has been passed down from generation to generation. In fact, a post-Civil War survey showed that many African Americans believed that they would be experimented upon if they entered hospitals (7).

In the modern era, disclosure of the unethical methods used in the Tuskegee Syphilis Study served to validate African American fears of experimentation and genocide. The Tuskegee Study involved the United States Public Health Service, the Tuskegee Institute, the Macon County Medical Society, the state and county Boards of Health and the Milbank Memorial Fund, as well as local black churches and public schools. Three hundred ninety-nine black sharecroppers were enrolled in the study in order to document the natural history of syphilis. The sharecroppers were not educated about the sexual transmission of syphilis or the vertical transmission from mother to fetus. The men in one arm of the study were excluded from treatment even when penicillin became the standard of care for syphilis in 1951 (8). In 1972, public condemnation of the Tuskegee study forced its termination almost forty years after initiation.

Although AIDS still raises suspicions of genocide in the minds of many African Americans, the impact of the epidemic has energized the community at the grassroots level. With this added energy and the allocation of financial resources, HIV prevention and screening programs are being conducted in churches, nightclubs, bars, barber shops, crack houses, and in various other community settings. These efforts have led to increases in the number of women reporting having had HIV screening and to small but significant decreases in the reported incidence of AIDS and AIDS-related death among blacks (9). Instead of featuring articles about AIDS as a genocidal plot, we now have articles such as "AIDS: The second wave," with positive reflections of individuals living with AIDS and information on HIV resources available to the community (10).

We are entering an era where significant decreases in AIDS transmission and mortality are being accomplished through prevention programs and highly active antiretroviral therapy. As physicians, we must be mindful to maintain ethical standards wherever and whenever we conduct clinical trials, and to secure and maintain the trust of the community.

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Resolving Conflicts:

Misconceptions and Myths in the Care of the Patient with Sickle Cell Disease

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Abstract

Sickle cell disease is an autosomal recessive disease that primarily affects persons of African ancestry. The hallmark of the disease is hemolytic anemia and vaso-occlusive crisis. Patients often have recurrent and severely painful episodes that necessitate the use of opioids. The reluctance of some health care providers to prescribe narcotics has resulted in adversarial relationships with some patients. The socio-cultural disparity between patients and providers may play a role. However, the lack of knowledge and understanding of the underlying pathophysiology of the disease and pain are the key issues. Education, research and hands-on experience, resulting in changes in attitudes and behaviors, will ultimately lead to a more empathic approach to the sickle cell patient. **Key Words:** Sickle cell disease, opioids, vaso-occlusive crisis.

Background

SICKLE CELL DISEASE is an inherited disorder that is characterized by altered amino acid composition of the globin chain. While the presence of sickle cell disease most commonly affects persons of African descent, it can also occur in people from the Mediterranean region. The gene frequency in African Americans is about 8%, but may be as high as 50% in equatorial Africa. Approximately 1 in 500 African Americans is affected with a sickle hemoglobinopathy. Currently, 220 patients with sickle cell disease (150 children and 70 adults) receive their care at the Mount Sinai Medical Center. Of these, 80% are African and Caribbean American, and about 20% Latino.

Hemolytic anemia and vaso-occlusion are the hallmarks of this disorder. Vaso-occlusive events may occur acutely or may be recurrent. These events can be quite frequent and severe, and when they occur in vital organs they can be life threatening. There can be considerable variability in the clinical course of different patients with sickle cell disease, and even—at different times—in the same patient.

A discussion of the mechanism and pathogenesis of vaso-occlusion is beyond the scope of this paper. However, there is increasing evidence that several factors, such as erythrocyte-endothelial interactions, vascular modulation, as well as hemostasis may play a role in the vaso-occlusive phenomenon (1). Genetic modifiers such as co-inheritance of thalassemia and fetal hemoglobin expression may also influence clinical expression.

Discussion

The acute, painful "crisis" accounts for most of the hospital visits of adult sickle cell patients. Because of the risk of overwhelming infections in the pediatric patients, episodes of fever account for a considerable number of pediatric visits. In most patients, there is no obvious precipitating factor for a painful crisis. In some patients, infec-

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tion, extremes in temperature, and physical or emotional stress may precipitate a crisis.

The pain typically involves the back, extremities, chest and abdomen but may occur anywhere. It is important to note that, in many cases, pain can and does occur without objective physical signs. The severity and frequency of pain can vary considerably among patients and sometimes in the same patient. Interestingly, the pain rate (i.e., the numbers of episodes per year) has been shown to be a good measure of clinical severity and a predictor of early death in patients over 20 years old (2). About a third of all patients with sickle cell disease have recurrent vaso-occlusive crisis, and only a very small percentage (5–10%) of patients experience more than 10–20 events per year (3). Although acute, recurrent, painful episodes are often the predominant feature of this disease, it should be underscored that sickle cell disease is not a one-dimensional disease. The frequent need to use narcotics to treat severe pain often leads to drug dependence in some patients which results in their stigmatization by some health care professionals. What role, if any, do these factors play in cultivating misconceptions, myths, misallocations and distrust?

The acute painful episode is frequently the principal complaint that leads the sickle cell patient to interface with the health care system. Perhaps the best approach to understanding the origins of these myths and misconceptions, stereotyping and stigmatization would be to focus on the issues of pain and pain management. It might be helpful to examine certain elements that may be a source of the friction with this particular patient group.

Both the patient and health care provider must understand the management of sickle cell pain. Negative attitudes about narcotics and fears of addiction may bias both providers and patients, which results in the failure to use opioids appropriately. In addition, patients may not have the skills needed to cope with a chronic, incurable disease. Feelings of helplessness, which often surface in early childhood or adolescent years, can lead to maladaptive behavior. This is frequently manifested during encounters with the health care system. Several fundamental questions should be addressed:

- What is the knowledge and understanding of sickle cell disease among health care providers?
- Do health care providers have a basic understanding of the pain of sickle cell disease?
- What is the patient's understanding of his/her disease?
- Since this is a disease that affects the entire family and support system of the patient, does the health care provider understand the psychosocial background of the patient?

In this discussion, we will attempt to address how and why these issues may impact on the provision of adequate and effective treatment for this group of patients, and propose strategies that may assist the medical community in developing a more candid relationship with the sickle cell patient.

Understanding the Pain of Sickle Cell Disease

Health care providers often fail to appreciate that there are different types of pain syndromes that occur in patients with sickle cell disease. Table 1 lists the different types of pain that a sickle cell patient might experience (4). It is important to recognize and appreciate these differences, because acute painful episodes are unpredictable in onset and severity.

Sickle Cell Pain

Many health care providers mistakenly believe that all pain is the same and, therefore, can be treated the same. But, pain research focused on the neurobiology of pain has established that the pathophysiology of pain in sickle cell disease is quite different from that of other pain syndromes. Ballas et al. have discussed this in detail (4). The standards and guidelines in the management of pain in patients with cancer and other pain syndromes are well established and have been widely published. These guidelines are helpful tools in the management and appropriate

TABLE 1
Types of Sickle Cell Pain

- Acute
  - Painful crisis
  - Acute chest syndrome
  - Right upper quadrant pain
    - Cholecystitis
    - Hepatitis
  - Priapism
  - Dactylitis (Hand Foot Syndrome)
  - Splenic sequestration

- Chronic
  - Avascular necrosis (hips/shoulder)
  - Vertebral collapse
  - Leg ulcer
  - Arthropathy
  - Arthritis

use of opioids and other analgesics for chronic pain of a finite duration. They do not, however, address the issue of the recurrent or chronic pain that is unique to sickle cell disease. The frequent, recurring and often chronic pain experienced by sickle cell patients sets it apart from many other pain syndromes in that this disease is lifelong and for most patients incurable (5).

Believe the Patient

The report of pain by any patient must be considered accurate. If the patient believes that he or she is not being taken seriously, and the physician is suspicious of the patient's motives in seeking care, an adversarial relationship is quickly formed.

Although this principle of trust in one's patient is crucial, it does not exclude a need for caution. Because the pain that some patients experience is chronic, the misuse of opioids does become a potential risk. Tolerance and sometimes dependency can become real problems. One contributing factor may be the lack of understanding of pain management by both the provider and the patient. To circumvent these problems, the use of adjuvant non-opioid analgesics, pain diaries, patient care contracts and non-pharmacologic methods (relaxation and diversion methods) have proven helpful for some patients. Patients who exhibit problem behaviors and those who tend to overutilize emergency room services should be identified. It is essential that each patient be evaluated and assessed on an individual basis.

Failure to Assess Pain Accurately

Accurate pain assessment is critical for adequate treatment of acute and chronic pain. Improper assessment of pain and failure to monitor the response to therapy are major factors in the failure to relieve pain. Patients are very different from one another in their clinical presentations. A patient who has infrequent painful episodes and who is considered "opioid naive" may require much less analgesic to relieve pain than someone with frequent episodes, who might be "opioid tolerant." Pain scales that allow a thorough evaluation and assessment of pain should be used; they may help to alleviate conflicts over appropriate dosage.

"Good Sickler"/"Bad Sickler"

For many patients with sickle cell disease, pain is part of their daily lives. This can indeed lead to misuse of the opioid therapy prescribed. Such misuse, in turn, can lead to tolerance, dependency and overutilization of hospital services by a very small subset of sickle cell patients. This group of patients generally accounts for many hospital emergency room visits. These patients, often labeled "drug seekers," can induce the staff to form false beliefs about all sickle cell patients. Such stereotyping interferes with the adequate and effective treatment of pain for other sickle cell patients. The failure by health care providers to distinguish between addiction, dependence and tolerance is a major component in the failure of effective management of the sickle cell patient with pain. It can lead to conflict and adversarial relationships.

Strategies to Improve the Provider-Patient Relationship

Most hospitals subscribe to and display a patient's bill of rights. Recognizing a patient's rights and clarifying patient responsibilities are paramount for improving the provider-patient relationship.

Patients have the right to:
- Considerate and respectful care.
- Confidentiality and privacy.
- Current information regarding their management.
- Participate in the planning of their care (unless it is judged unsafe for them to do so).
- Informed consent.
- Refuse treatment.
- Voice grievances about care or services.
- Continuity of care.

What role does the patient play in helping to dispel the myths and misconceptions about patients with sickle cell disease? A relationship that is grounded in mutual respect requires balanced input and therefore obligates the patient to uphold certain responsibilities.

Patients' responsibilities include:
- Providing, wherever possible, accurate and complete information about their symptoms and medications to the various health care workers involved in their care.
- Complying with instructions given related to care and medications provided.
- Asking questions and participating in the planning of their care.
- Understanding the management of pain and the careful use of opioids and analgesics.

- Understanding the importance of establishing a trusting relationship with their provider (4).

Changing Attitudes and Behaviors

As health care providers, our attitudes and beliefs influence the relationships that we form with our patients. These beliefs affect the care and management we provide. Attitudes and beliefs about pain and pain management, particularly the use of opioids, are typically negative. Denial of the importance or presence of pain and fears of addiction are the basis for this bias.

How do we change attitudes and behaviors? One obvious answer is education. Curricula for physicians, nurses and other health care professionals have been developed by the International Association for the Study of Pain, and teaching materials are available (6). Table 2 lists several factors that affect the use of analgesic medications and possible strategies to change behaviors.

TABLE 2
Factors Affecting the Prescription of Analgesic Medications

Factors	Corrective Strategy
Denial of the existence of pain	Educate; change policies to require measurement of quality assurance of pain; file complaints.
Denial of the importance of pain	Monitor and record pain; educate about long-term effects of pain.
Unfamiliarity with effective use of analgesics	Pain management education.
Fear of adverse effects (e.g., respiratory depression and addiction)	Educate about extent and management of side effects.
Fear of scrutiny by regulatory agencies	Ensure that regulatory agencies are sensitive to management.
Family views	Examine underlying anxieties; give information.
Patient/family fear of tolerance, addiction and drug abuse	Patient/family education directed at false beliefs.

The Difficult Patient

As previously mentioned, a small subset of patients is difficult to manage and triggers negative reactions in some health care providers. Possible solutions for dealing with these patients include:

- Providing continuity of care by designating a single physician or health care team.
- Offering psychosocial support (i.e., family, other patients, support groups and psychiatric intervention).
- Designing patient care contracts that set limits.
- Designating a single pharmacy for prescriptions.
- Being consistent with the plan of care.

Conclusion

Sickle cell disease is an inherited chronic illness that carries the risk of significant morbidity and mortality. Lack of knowledge about sickle cell disease and the difficult issues of pain management lead to negative attitudes among providers toward patients with the disease. Through research and education, changing attitudes and behaviors will lead to establishing a more reciprocal relationship, and thus more effective management of the patient with sickle cell disease.

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Panel Discussion

Daniel Moros:

Professor Baker would like to make a few more remarks to follow up on comments made about his paper.

Robert Baker:

Conferences are dull when no one disagrees, but I didn't quite expect to encounter so much disagreement, so let me go back to where I started. I started on my computer by doing some standard computer searches on minorities in medicine. I hit pay dirt starting in 1980 with an extraordinary amount of material coming out of Washington from two data sources providing statistics on minority comparisons. The first thing that struck me about these data was that between 1900 and 1990, there was a convergence between minority populations and everybody else with respect to health care status. The big picture shows that the difference is becoming smaller and smaller. But if one looks at the details of the way in which the reports were constructed, they all focus, bit by bit, on differences in so-called minority/majority comparisons. This seems fair, given that in 1980 the goal to eliminate disparities was announced. However, around 1987, data on Cubans came out of the minority category, and then data on certain kinds of Mexicans. In fact, when a minority group's statistics really look good, they are promoted into the majority group, making the disparity look worse than it did before. I looked at the rhetoric and realized that the statisticians are, in effect, trying to implement an affirmative action kind of model. They want to get all the resources toward the least advantaged group.

At the same time, I was looking at who had been discriminated against in the long history of Western health care. While there is no category based on socioeconomic status, poverty is certainly coincident to those groups marked by the special language used to describe them. Marking groups by means of special language has became more and more prominent in the government's data. After I reread *Bad Blood*, the definitive study of the Tuskegee study, the fact that the *Journal of the American Medical Association* used the headline "Negro Males" stood out all the more. It was also telling that they were using a civil rights model in working through the health care data. This is indicative of a particular kind of danger. While this approach offers a short-term advantage (i.e., you get more money with which to benefit a disadvantaged group and, therefore, they are better off), in the long term there are disadvantages. People are marked in exactly the way racists mark them. We want to be very careful about that. I wondered whether we really wanted to superimpose an affirmative action model on public health surveillance. One of today's speakers has argued that we do. But in my view, a convincing case has yet to be made. We've got $400 million; let's put it to good use.

Leslie Pickering Francis:

Are we really looking at the issue of distribution? Or are we looking at socioeconomic status? Or do we have enough evidence to be suspicious that there is ongoing discrimination in treatment? I allied myself with those who suggested that there are actual differences in the health care encounters people have that still need correction. Some of those differences actually go both ways, because race-based reluctance to participate in medicine exists, as, for example, with Dr. Burrows's discussion about kidney donation. One of the reasons I didn't use the renal transplant data is because if you only glance at the data, it looks as if blacks get fewer transplants. However, a careful review of the data reveals a reasonable explanation. Blacks have poorer tissue matches as a result of donation patterns. So, my suggestion is to look to education. Notice, however, that this too takes race-based action.

Lewis Burrows:

What Maritza Rozon-Solomon and I tried to present was a slightly different perspective. In our field, 99.9% of the time a computer selects the person who will get a given organ. The distribution system is based on a point system which is considered to be fair. Our presentation differs slightly from others by showing how distrust of the system in general affects not only the individual but all members of the same race. African Americans are being denied transplants because members of the African American community, who are well matched for histocompatibility with the African American patients currently on dialysis, are not offering their organs. Thus, they are affecting all people by their refusal to donate. In terms of the allocation system, we've tried to derive a very fair, unbiased method. A current concern in the transplant community is how to enable more kidneys harvested from Caucasians to be used in transplantion to African American patients. This would enable more African Americans to have transplants sooner than is currently possible. However, kidneys harvested from Caucasians don't do as well in African Americans as would kidneys harvested from other African Americans. Changing the formula would result in a form of reverse discrimination. It would mean that more kidneys harvested from Caucasians would go to African American patients, where they would not do as well as they would if used for transplant to Caucasians. Rather than do this, the push should be to educate the African American community at large to donate organs. If this were to happen, both African Americans and Caucasians would benefit.

Moros:

Dr. Burrows, perhaps the issue you raise spans this entire discussion. Some of our speakers have talked about public policy, others, personal experience in health care. You have described your personal experience with distrust. It has a public policy challenge embedded within it. I wonder if any of the other speakers would like to address the connection between personal experiences of conflict and distrust, and some of the public policy issues?

Chen-Li Sung:

I think Professor Francis raises a very good point, which is, distrust can be taken to another level. It is not simply distrust during an encounter, but distrust of the physician's conduct at the level of treatment, and judgments about which treatment or procedures should be done. So, a question for Dr. Burrows is, do you think physicians and transplant surgeons are the ones who should decide which numbers and scores should be fed into the computer? Or, as Professor Francis describes it, can a case be made that surgeons are making race-based decisions that then affect the protocol?

Burrows:

It can't be done. It's virtually impossible to do that at this point. Let Ms. Solomon describe how we feed the data into the national data base computer on any single patient who comes into our clinic wishing to have a kidney transplant.

Maritza Rozon-Solomon:

The data that's put in is scientific data, not anything that can be manipulated. It's DNA testing tissue typing. We put in the patient's red blood cell blood type, and the computer calculates on a daily basis how long the patient has been waiting. The clock starts ticking from the time the patient is activated on the computer. That's all that is fed into the computer. Also, once a month we input the current sensitization of the patient, i.e., how many cytotoxic cells the patient has in circulation.

Lynne Richardson:

What about the decision that gets made to put someone on the list?

Rozon-Solomon:

So far, that has not been discussed today. The criteria being used to accept candidates into the system have much more leeway in terms of who gets accepted and who does not. Transplant centers are now accepting more high risk patients, e.g., diabetics, hypertensives, and cardiac cases. These patients have a much higher risk of not making it past the first year post-transplant and dying with a functioning kidney. Since dialysis can maintain such patients and keep them alive, kidney transplantation is more a quality-of-life issue than one of life and death. However, giving such patients a kidney, a scarce resource, is taking it away from someone who would doubtless have a much better outcome.

Francis:

It might be interesting to try to see whether there is reverse discrimination in the decision that you get a score of such-and-such for such-and-such an antigen match. We might consider the possibility of reverse discrimination in altering transplant criteria to accept higher risk patients. I'm not suggesting that the actual data you feed into the computers isn't scientific, but the interesting question concerns how you then evaluate that data with respect to scoring.

Rozon-Solomon:

At the moment, the specificity test on which basis they give points for tissue typing is based on an identical match, e.g., an A for an A and a B for a B. What the United Network of Organ Sharing (UNOS) is proposing instead is, an A1 will be able to match 10 different other specificities, which are not being matched right now, thereby increasing the number of people who will match a given kidney.

Audience:

I wonder whether we've reached a point in this country where our fondness for transplantation and our preoccupation with high tech medicine is somewhat misplaced. If we're talking about saving lives, one could argue that our focus on saving the lives of people who can't afford the fees is one concern that should be put in the larger context. We should be doing more in terms of prevention and providing health insurance, so we can keep people from having uncontrolled hypertension, for example. If we're going to talk about what's of benefit to minority populations, having health insurance for everybody is a major issue. It would benefit a greater number of people. One wonders how we can improve trust in the doctor-patient relationship when we live in a society that doesn't even guarantee access.

Burrows:

You're not going to get an argument from me. I've devoted most of my professional life to transplantation. It is a very expensive modality for a relatively small percentage of our population. When the federal government decided to select out one disease entity—end-stage renal disease—and provide total care for that group of patients under the Medicare system of the Social Security Administration, that was unique. It's never been done before. What they first projected as costing $12 million a year is now costing $3 billion a year. If you want the best for your buck, obviously you wipe out transplantation; it's not really providing that much for that many people. It's a sexy field, it's fun, it's exciting, but if you have a limited amount of money you want to distribute, I would distribute it along the lines that you mentioned: education, preventive health care and the like.

Rosamond Rhodes:

Dr. Schonholz, we have heard a lot about the need for sensitivity to cultural difference, and your program is sensitive to the Jehovah's Witness religious conviction of refusing blood transfusions. I imagine that costs a lot of money. Can you tell us something about the comparison of costs for a normal delivery and the problematic delivery of a Jehovah's Witness? Who is responsible for the extra costs?

David Schonholz:

The Jehovah's Witness community has attempted to solve their problem on a financial basis. Approximately eight years ago, they realized that they were bringing their health care dollars to all the major institutions. But what has happened is fascinating. They've taken the bull by the horns and decided to send Jehovah's Witness patients only to hospitals that are attentive to their concerns about blood and to recommend only those physicians who honor their precepts.

Rhodes:

I'm interested in how much more it costs for bloodless treatment and who pays for it. If my religious conviction is to have kosher beef, I pay for it. If somebody else's religious belief only permits bloodless surgery and it costs three times more, is that person paying for it or are we all paying for it?

Schonholz:

At the present time, a large portion of the Jehovah's Witness population is covered by Medicaid. So, ultimately it is the government which supports it. However, in the last five years, the Jehovah's Witness religion has put in a self-insurance program for their own support. Their reimbursement is not as great as with other plans, and patients on their plan may have to seek out hospitals and physicians that will accept their reimbursement.

Rhodes:

And do bloodless procedures cost more?

Schonholz:

In actual costs, it is more. The use of a cell saver, for example, would be an added expense, so the dollar cost is more.

Audience:

We've skirted around this issue, but in what sense does ability to pay enter into this whole discussion, and has that been part of this whole issue with discrimination? Also, how has managed care impacted on minorities in the health care system?

Rozon-Solomon:

For any kind of transplant program, financial screening is geared toward whether or not the patients will be able to afford the lifelong immunosuppressive medication. There is no use giving patients transplants when they are not going to be able to maintain it. Patients who have Medicare or Medicaid are eligible from a financial standpoint. Reimbursement to the hospital and to physicians and for other costs may not be as great as it would be, for example, with Oxford or Aetna, but the patients will be accepted and transplanted. Our focus is on assuring that patients can afford the medications. Three years after a transplant, Medicare no longer covers the immunosuppressive medications. How is the patient going to pay for them? The medication can cost anywhere from $600–$1000 per month. If the patient can't afford that, we are doing an injustice by giving him or her a transplant.

Ian Holzman:

For kidney transplants, the ability to get money to pay for immunosuppression medication long term is an issue, but it isn't true for liver or other organ transplants. Medicare will only pay for the immunosuppressive medicine necessary to sustain a kidney transplant for a limited amount of time.

Burrows:

If you want a transplant, the best thing you can have is Medicaid. It provides lifetime support for your transplant. The worst situation is a middle-class person who has limited health care insurance.

Schonholz:

And if you want to have a cell saver and no transfusion, the best thing to have is Medicaid and an institution that will make adjustments to its budget to support the management of this type of patient.

Cheryl Smith:

I was going to make a comment about HIV disease. New York State happens to be very generous when it comes to HIV disease. If a patient comes into whatever system, New York State has an AIDS drug-assistance program that allows us to provide medications and some other limited services for the patients, as well as medical services. It's more limited than Medicaid, but for a short period of time and if the patient does not quality for Medicaid, the patient is able to take advantage of the program.

Richardson:

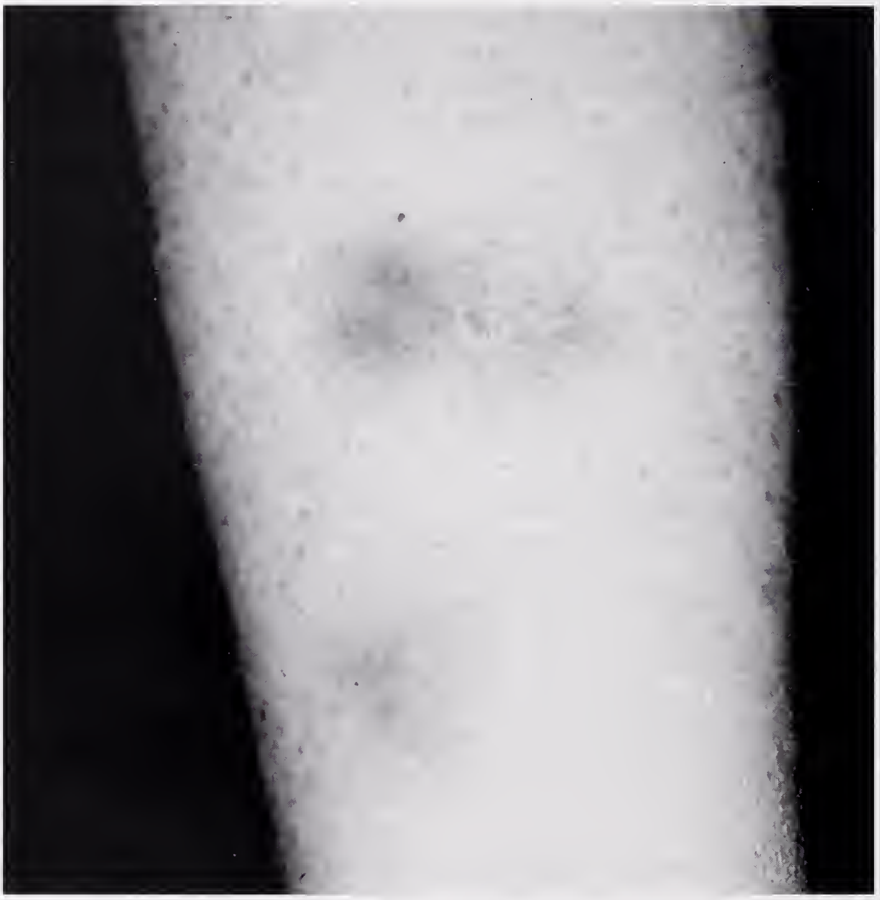
I'd like to give a more general response to the question of how ability to pay affects access to care. In fact, this could be the subject for another conference. I don't think there's any question that the ability to pay is central to everyone's ability to get access to care in this country, be they white, black, brown, etc.—it doesn't matter. Clearly, though, racial minorities are more likely to be in the category of people who are unable to pay, so those financial barriers affect them disproportionately.

On a daily basis, I now see individuals who are in need of health care for which they have no ability to pay. Once they get below the level of a true emergency, I'm unable to obtain treatment for them through the Emergency Department. For example, I see patients with high blood pressure who cannot afford the medications needed to control their blood pressure. When they come back with a stroke or heart attack, however, we do pay to take care of them. This is part of the whole issue about what kinds of health care we ought to pay for. This is especially true, given that much of our available resources is concentrated on inpatients and end-of-life care, and so little is provided for prevention and health promotion programs. These are not only morally questionable decisions and practices, but they are bad medicine, and reveal an unenlightened social policy.

It's true that if you are not well off, the best insurance you can have is Medicaid. The worst position is slightly above the level of poor enough to qualify for Medicaid. This is the situation of part-time workers or those who have a full-time job in a small business that offers no health care benefits. In such cases, there is no access beyond emergency care. I've seen young people with disabling injuries who can't get semi-elective orthopedic procedures because they have no insurance and cannot afford to pay for the procedures themselves. Given my personal experience with such public policies, I don't understand why we tolerate the system.

Dermatology Notes

Erythema Nodosum



A SEPTAL PANNICULITIS results in this disorder, which has been attributed to inflammatory bowel disease, sarcoidosis, tuberculosis, and other infections, Behçet's disease, numerous drugs, and pregnancy.

—Albert M. Lefkovits, M.D., Marsha Gordon, M.D., and Mark Lebwohl, M.D.

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Dean's Lecture

The Telomere and Telomerase:

How Do They Interact?

Elizabeth Blackburn, Ph.D.

Abstract

The ribonucleoprotein (RNP) enzyme telomerase synthesizes telomere DNA and maintains telomere length in eukaryotic cells. This review describes recent findings that provide new understanding of the functions of telomeres and telomerase. Telomerase has an essential RNA moiety in which a short sequence acts as the template for synthesis of telomeric DNA. Recent results show that, besides acting as a template, the telomerase RNA plays essential roles in the enzymatic functions of telomerase that are as critical as those provided by the protein reverse transcriptase subunit of telomerase. Analysis of telomerase RNA mutants in yeast has provided evidence that telomerase is an oligomeric/dimeric enzyme containing at least two telomerase RNA molecules and two enzyme-active sites. Recent data suggest that this telomerase RNP also plays a critical role in capping short telomeres. Thus, the length of a telomere is only one determinant of whether it is sufficiently long to function as a cap, stabilizing the chromosome end. Several lines of evidence converge on the notion that for telomere length regulation and other telomere functions, the very few last repeats at the tip of the telomere are the most crucial. **Key Words:** Telomere, telomerase, human telomerase, yeast telomerase, telomere homeostasis, *Kluyveromyces lactis, Saccharomyces cerevisiae, Tetrahymena thermophila.*

Introduction

All chromosomes in a typical eukaryote bear telomeric DNA at their termini. The amount of telomeric DNA varies from telomere to telomere but is kept within well regulated upper and lower bounds. What are telomeres for? First, they cap the ends of the chromosomes. This capping function includes shielding the telomere from being recognized as damaged DNA, thus causing cell cycle arrest, and shielding telomeres from engaging in inappropriate kinds of recombinations. Capping also protects the telomeric DNA from degradation. In addition, the conventional cellular DNA replication machinery alone appears unable to replicate telomeric DNA completely. This creates a need to top up the telomeres frequently to compensate for this lack of complete replication, and perhaps also to augment DNA lost through nuclease action at telomeres. A major player in the replenishment process is telomerase, as described below. We still don't know all the molecular answers to how capping and replenishment are accomplished. One newly recognized aspect of telomeres that will be emphasized in this review is that both the telomerase ribonucleoprotein (RNP) itself, as well as the very last few telomeric repeats on the chromosome and their associated proteins, are emerging as critical molecular and functional components of the chromosomal cap.

The telomeric DNA sequences of eukaryotic linear chromosomes are repeated sequences, examples of which are shown in Fig. 1. The number of repeats per telomere varies greatly from organism to organism. For example, the ciliated protozoan *Tetrahymena thermophila* has about 50 T_2G_4 repeats whereas humans and many other species have up to thousands of T_2AG_3 repeat units per telomere. Somewhat different-looking repeat sequences are found in *Sac-*

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Tetrahymena	**TTGGGG**
Vertebrates	**TTAGGG**
S. cerevisiae	**$(TG)_{1-6}TG_{2-3}$**
K. lactis	**ACGGATTTGATTAGGTATGTGGTGT**
C. albicans	**ACGGATGTCTAACTTCTTGGTGT**

Fig. 1. Telomeric DNA sequences.

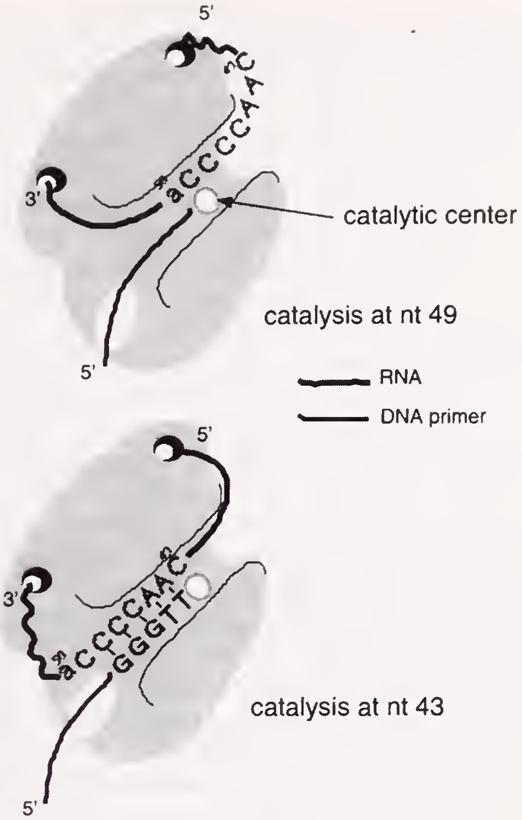

Fig. 2. The basic core machinery of telomerase in the ciliated protozoan, *Tetrahymena thermophila*.

charomyces cerevisiae — with its somewhat less regular repeated sequences — and *Kluyveromyces lactis* — another budding yeast related to *S. cerevisiae*, which has a rather long, 25 base-pair repeat unit. Both yeasts have telomeres that are a few hundred base pairs in length, whereas typical human telomeres are thousands of base pairs long. The enzyme telomerase specifies and synthesizes the unit repeat sequence of the DNA strands shown in Fig. 1. Although these sequences differ somewhat from each other, it is becoming very clear that, fundamentally, telomerase and telomeres function very similarly in these different species. The findings from experiments done in the simpler model organisms, therefore, have important implications for humans. We have chosen various systems for the experimental ease by which we can explore certain aspects of telomere function. Some of the experiments described here will be drawn from *Tetrahymena*, others from *S. cerevisiae* or *K. lactis*, and yet others from humans cells. Both new and older results emphasize the role of RNA in the capping and DNA synthetic functions of telomerase.

The Roles of Telomerase RNA

Fig. 2 illustrates the basic core machinery of telomerase in the ciliated protozoan, *Tetrahymena*, and its mode of reaction. *Tetrahymena* telomerase was the first telomerase to be discovered, by Carol Greider and me at the University of California, Berkeley, in the mid-1980s (1). Depicted in Fig. 2 is the end of the chromosomal DNA, which has a duplex region, and in at least some fraction of the DNA, an overhanging DNA strand. The 3' end of this overhang, consisting of the T_2G_4 repeat sequence, can be elongated by the addition of nucleotides, using dNTPs as substrates. Elongation occurs by copying a template sequence that is part of the telomerase RNA moiety of this RNP. We showed some years ago that by making mutations in the template sequence we could change the complementary sequence in the telomeric DNA (2, 3).

The core RNP of the telomerase complex contains a reverse transcriptase protein component, with amino acid motifs characteristic of the reverse transcriptase family (4). These include three aspartate residues that form the catalytic metal-binding sites for the catalysis of polymerization.

Telomerase RNA, in addition to providing its well documented templating function in this and other species' telomerases, also has some very interesting roles in the action of telomerase. These roles have important mechanistic implications for how the active site of this RNP enzyme works, as well as interesting evolutionary implications. Telomerase RNAs vary greatly in size among different species, with the smallest (about 150 nucleotides long) being in the ciliated protozoans, ranging through about 400 nucleotides in mammals, to up to 1.3 kilobases in yeasts such as *K. lactis* and *S. cerevisiae*. There is also an enormous range in primary sequence: within the ciliated protozoa alone, for example, the RNAs diverge by more than 80% in primary sequence. However, ciliates share a remarkably conserved core secondary structure. This, together with the data described below, is consistent with the telomerase RNA playing important roles in the active site functions of telomerase (5, 6).

David Gilley in our group first analyzed the *in vitro* telomerase activities of telomerase containing telomerase RNAs bearing various template mutations (7, 8). Strikingly, he found that making specific changes in the template caused remarkable changes in the way that the enzyme acted. For example, a C to U mutation at position 48 — a tiny change of just an amino group to a keto group on the base at that position — had drastic effects *in vitro* and *in vivo* (2, 7). The wild-type enzyme synthesizes many tandem 6-base T_2G_4 repeats *in vitro*. In contrast, the reaction catalyzed by the 48U base substitution mutant enzyme sputters out very quickly. Through extensive analyses, we concluded that this mutant enzyme breaks some of the cardinal rules for nucleic acid polymerases that perform template-directed synthesis: it has very low fidelity at certain places on the template, misincorporating at rates approaching 50%, even at low triphosphate concentrations *in vitro*. To put this result in perspective, the HIV reverse transcriptase, and other viral reverse transcriptases that are notorious for their low fidelity, have error levels of only 10^{-2} to 10^{-3}. Not content with that, once the 48U mutant telomerase misincorporates, producing a mispair, unlike any good polymerase that will reject the mispair for further elongation, this mutant telomerase continues to elongate it. Another telomerase RNA template mutant behaved similarly. In addition, certain template mutants make slippage errors, reiterating the copying of some template nucleotides (2, 7). The 48U mutation and some other template mutant enzymes also dissociate the DNA product too quickly from the enzyme, aborting synthesis (2, 8). In summary, template mutations can produce dysfunctional enzymes.

In vivo studies reinforced the conclusion that the 48U mutant enzyme functions poorly. This mutation caused the telomeric DNA to shorten, and after about 20–25 cell divisions the cells stopped dividing (2, 7). Expression of this mutant RNA provided the first demonstration in any system that telomerase is important for cells and that functional telomerase is required for cells to continue dividing (3).

Similar and even more dramatic phenomena were seen by mutating the large yeast telomerase RNAs (9, 10). John Prescott in our lab group made mutations in the template sequence of the telomerase RNA of *S. cerevisiae*. The templating domain sequence of this species' RNA contains some redundancies that may partly account for the irregularity of the sequence made *in vivo*. John made a series of trinucleotide substitutions both in and next to the template region. When he assayed the *in vitro* enzymatic activity of telomerase containing these substitutions, one of them, called 476GUG, had no telomerase activity. The 476GUG mutant RNA was stable, transcribed and expressed normally, and formed in an RNP particle with the same chromatographic and size properties as normal telomerase. Thus there is nothing obviously wrong with the assembly of this telomerase, leaving us with the conclusion that the problem lies at the level of enzymatic action itself (11, 12).

Similar results were found by Jagoree Roy and Tracy Boswell Fulton in our lab group for the large telomerase RNA of the related yeast *K. lactis*. In this case, changing just a few bases located several hundred nucleotides away from the template produced a completely inactive telomerase enzyme. Again the RNA was stable and assembled into a stable RNP. Emphasizing the specificity of this result, we found that various large deletions of other portions of this RNA caused no problems for enzymatic function (13).

In summary, small changes in the sequence of even very large telomerase RNAs can have a dramatic impact on the telomerase RNP enzyme. I would like to put these results into perspective with respect to our views of enzymatic active sites. A component of a protein enzyme required for the active site of that protein is typically defined by, for example, mutating catalytic aspartates to alanine, as was initially done for the yeast telomerase reverse transcriptase protein component (14). Such a mutation destroys the catalytic activity that produces the phosphodiester bond, as one would expect. However, in addition to catalysis, the active site also has other functions: for example, it has to bind triphosphate substrates, along with the template and primer, and then carry out whatever conformational changes are necessary to get the catalytic aspartates in position to execute the reaction. Notably, as described above, specific small changes in the RNA, as opposed to the protein, of telomerase produce the same result as mutating the aspartates — no enzymatic activity. Therefore, even when the protein is intact, highly specific mutations in the yeast telomerase RNA can prevent the active site from functioning. We normally imagine that an active site is built up through a network of interactions between amino acids in a protein. Here, we propose that the RNA residues also play crucial roles in building up the network of functional interactions. Together, these place the catalytic aspartates in the correct configuration for activity. Therefore, we propose that the active site of telomerase is composed of various functional groups contributed by RNA telomerase as well as protein residues.

The RNP structure of telomerase presents another interesting problem for a nucleic acid polymerase. The template sequence is only a very short, exposed part of the larger RNA that is built into the RNP particle. The template is anchored into the RNP in some fashion. At the beginning of a round of elongation, the DNA primer and built-in template have a particular spatial relationship to the protein's catalytic center. But as polymerization occurs along the template, the primer-template moves past the catalytic center, changing the relationship of the built-in RNA to the protein in the RNP (Fig. 2). Thus, effectively, a new active site is created for each new polymerization step. Perhaps the protein cannot by itself make this new active site at every step, and is helped by the RNA, as described above. The notion of building a new active site at each polymerization step may account for the observation that the properties of the enzymatic reaction are very different at each step of the polymerization — i.e., are template position-specific — during copying along the template (15, 16).

A Telomere Capping Function for the Telomerase RNP

Chromosomal ends are protected from being recognized as damaged DNA, from undergoing inappropriate recombination and from being degraded. Our recent work suggests that the telomerase RNP itself helps provide that protective function. First, the telomerases of two yeasts, *S. cerevisiae* and *K. lactis*, act highly nondissociatively when elongating a telomeric DNA primer *in vitro* (12, 17). In other words, the telomerase stays bound to its DNA product. Hence, these telomerases produce very short products *in vitro*, not because the enzyme is destroyed or degraded after a round of synthesis, but because the product stays associated with the active site and cannot be further elongated. One of the experiments that showed this was simply to allow the reaction to take place, then use gel filtration chromatography to attempt to separate out the telomerase RNP particles (plus any of their bound products) from free DNA products (whose expected fractionation properties were indicated by synthetic oligonucleotide markers). The products of the telomerase reaction remained associated with the RNP. This result suggested the possibility that *in vivo* telomerase may also be associated with its DNA product, the tip of the telomeric DNA (11, 12).

Other findings supportive of a capping function for telomerase were made *in vivo*. Deletion of the telomerase RNA (so there is no telomerase RNP in the cell) causes *RAD52*-dependent recombination to occur at telomeres, even those that are very long (18). This suggests that recombination doesn't normally take place at telomeres, but in the absence of a cap — that is, the absence of any telomerase RNP — recombination can act rather promiscuously on these telomeres.

Another indication of a capping function for telomerase came from experiments with the *S. cerevisiae* template mutations described earlier (11, 12). Unexpectedly we found that the 476GUG mutation, which is unable to carry out polymerization, causes loss of cell viability and senescence to occur sooner than expected if telomere length alone were important. In this mutant, telomeres progressively shorten. Senescence is interpreted to be the response to the DNA damage signal resulting from uncapped (shortened) telomeres. Certain other telomerase RNA mutations, in and outside the template, also cause telomeres to shorten. However, in contrast to the 476GUG mutant, the telomerase in each of these other mutants, although somewhat altered in its action, is enzymatically active, and the cells continue to grow perfectly well with no sign of senescence (11, 13, and yet-unpublished work by J. Roy and E.H. Blackburn). The striking finding was that the telomeres in these actively dividing mutant cells were considerably shorter than those in the (otherwise isogenic) 476GUG mutant at the time of its senescence.

We proposed that an active telomerase may bind to its product, the telomeric DNA, as it does *in vitro*, and thereby help to stabilize short telomeres (12). Thus telomere length is not the sole determinant of when senescence will occur. This is relevant to the situation in human cells. As a very broad-brush generalization, cancer cells often have active telomerase, and their telomeres are maintained to at least some degree, although their telomere lengths can vary. In contrast, many somatic cells lack active telomerase, although often cells that are proliferating or are in regenerating tissues do have it. In cells lacking telomerase, over the human lifetime telomeres generally shorten (19, 20). Thus, we can ask: is it the shortening of telomeres, the presence or absence of telomerase, or a combination of both that is important in signaling to cells when to stop dividing? Very recently, we showed in cells growing in culture, that it is the combination of both (21). We do not know if these findings are directly relevant to normal aging of the human body.

However, it was yeast, a very simple system, that clearly told us that it is not just telomere length per se, but rather a lack of active telomerase combined with some degree of shortening, that together determine when a cell will stop dividing.

Evidence for an Oligomeric/Dimeric Telomerase RNP

In the course of the yeast experiments described above, we obtained other surprising results that forced us to think about telomerase in new ways (11, 12). These results came initially from yeast genetic experiments involving mating the 476GUG mutant cells to wild-type cells and analyzing the resulting cells that now contained both wild-type and 476GUG telomerase RNAs. The 476GUG RNA-containing telomerase, which had been completely inactive when only the 476GUG RNA was present in the cells, now sprang to life! Cloning and sequencing of telomeres synthesized in these heterozygous cells showed that the 476GUG telomerase RNA template (as well as the wild-type template) was now copied into DNA. The classic genetic way of explaining such a result was that the telomerase enzyme works as an oligomer, minimally a dimer, in which the wild-type telomerase RNA is able to rescue the 476GUG RNA function. Through *in vitro* biochemical experiments, we established that this is the case, and that the active telomerase RNP particle minimally is dimeric, with two telomerase RNAs and two enzyme-active sites. Furthermore, in order to be rescued by the wild-type RNA, the 476GUG RNA has to be in the same oligomeric/dimeric telomerase RNP complex as a wild-type telomerase RNA; if the oligomeric/dimeric complex contains only 476GUG RNAs, the 476GUG RNA cannot function (12). We do not yet understand the mechanism of the communication between the two RNAs, nor why 476GUG telomerase RNA cannot function by itself.

Critical Roles for the Telomeric Repeats at the Very Tip of the Telomere

In the last section of this article, I will focus attention on the very tip of the telomere itself. I will first briefly review our current views on the way telomeres regulate their length. In a population of telomeres, one observes a gaussian-like distribution of telomere sizes. This distribution, strikingly, has clear lower and upper limits (Fig. 3). We propose that a homeostatic mechanism normally acts at the level of the telomere to keep telomere lengths within these boundaries (22, 23). Although one can envisage a static model, an alternative dynamic model is currently borne out by much data. In this model, telomerase and the telomere act together as a homeostatic system consisting of both negative and positive regulators of telomere length. We can observe this active, dynamic balance in action in growing cells by making mutations in the telomerase RNA template (24). The appearance of mutant repeats can readily be monitored by, for example, placing a restriction site in the mutant repeat sequence, and following the encroachment of the restriction sites into the telomeres by digesting them with the restriction enzyme. Over time, the original distal repeats of the telomeres become replaced by mutant repeats. This addition is balanced by shortening, perhaps through incomplete replication, and/or nuclease action. The addition and losses occur somewhat stochastically, but normally are balanced overall, i.e., are in equilibrium. Hence, there is a continual dynamic turnover at the telomere tip, but the overall telomere length will stay constant (Fig. 4).

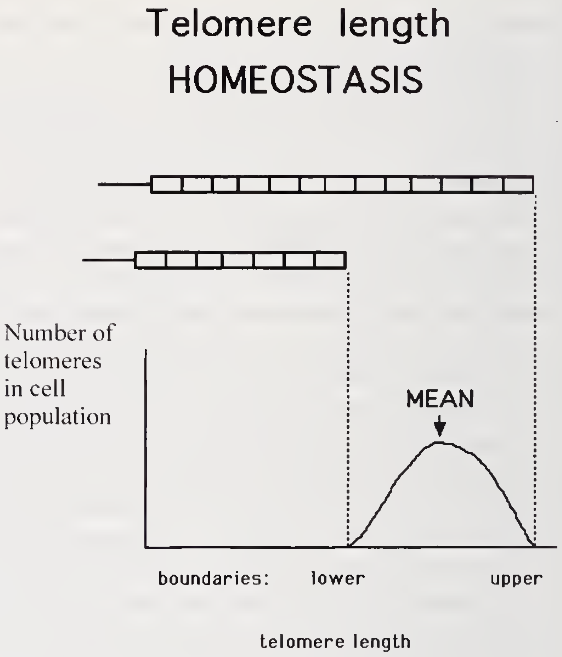

Fig. 3. Telomere length.

What causes telomeres to be so resistant to further shortening? Much work, done by our lab and by others, provides evidence that the access of telomerase to chromosomal ends is negatively regulated. The negative regulator is the telomere itself (24–27). In yeast, a key player is the Rap1p protein, a sequence-specific, double-stranded telomeric DNA binding protein. Rap1p

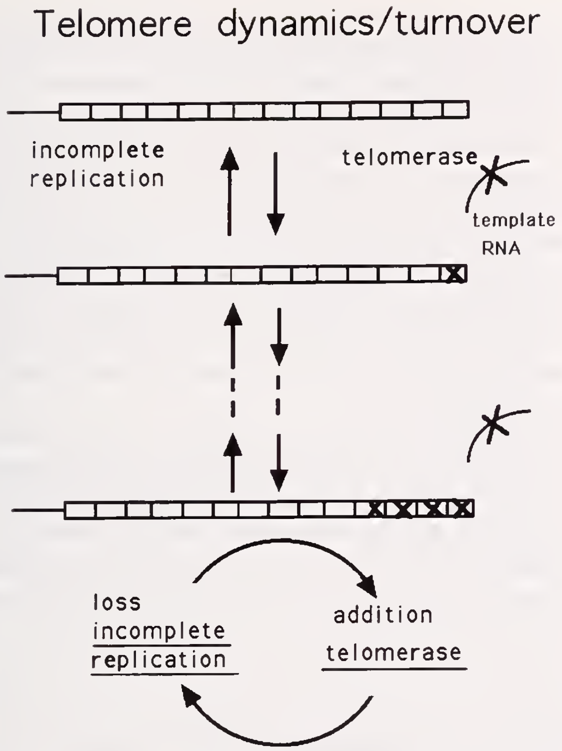
Telomere dynamics/turnover
incomplete replication
telomerase
template RNA
loss
incomplete replication
addition
telomerase

Fig. 4. Dynamic turnover at the telomere tip.

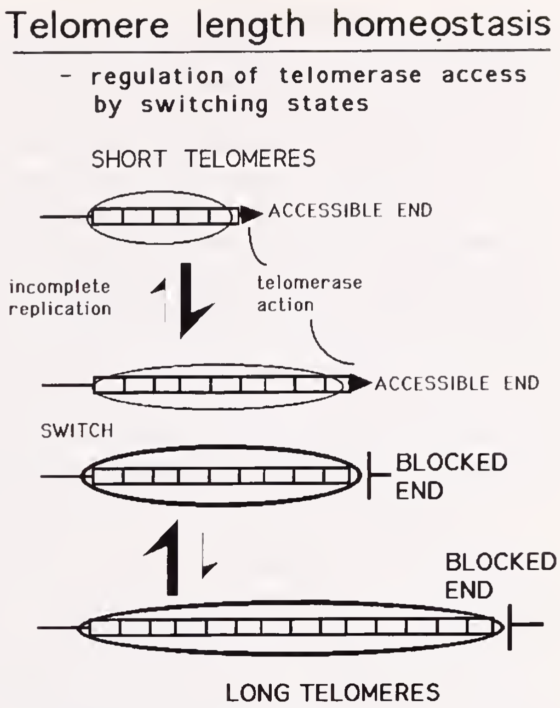
Telomere length homeostasis
- regulation of telomerase access by switching states
SHORT TELOMERES
ACCESSIBLE END
incomplete replication
telomerase action
ACCESSIBLE END
SWITCH
BLOCKED END
BLOCKED END
LONG TELOMERES

Fig. 5. Telomere length homeostasis.

coats the telomeric DNA repeats and then assembles around itself a suite of other proteins, thereby building up a higher-order nuclear protein complex. The C-terminal domain of Rap1p is used to organize the binding of the other proteins to the telomere, but has no effect on DNA binding per se (27). We proposed that this telomeric higher-order complex can switch between a telomerase-accessible and a telomerase-inaccessible state. This two-state model has the requisite features of a robust homeostatic system, based simply on the idea that enough telomerase is present and that the telomere itself can block the access of telomerase to the telomeric end (Fig. 5). Specifically, in this model the longer the telomere, the more likely it is to be in the inaccessible state. Conversely, the shorter it is, the more likely it is to be accessible to telomerase. Thus, the probability of being elongated with telomerase is high for short telomeres and low for long ones. When a telomere is long, telomerase will fail to add more DNA, and the telomere will gradually get shorter over time, increasing its chance of switching into the telomerase-accessible state, at which point the shorter it is, the more likely it is to be elongated.

One interesting consequence of such a homeostasis system is seen if one tries to break out of the normal boundaries, for example by manipulating telomerase activity in cells. We attempted to ablate telomerase activity in human lymphoid cell lines grown in culture. The goal was to shorten telomeres so they were no longer stably maintained, and thereby arrest cell division (28). The chain terminators AZT and dideoxy-guanosine, in their triphosphate form, partially inhibited human telomerase *in vitro*. These inhibitors of telomerase, when added to cells in culture in their nucleoside form, caused progressive telomere shortening over several cell passages. The telomeres then became stably short, but the cells kept dividing. Thus, the telomeres were very resistant to further shortening. By ablating telomerase activity only partially, it appeared that the telomere length equilibrium was reset to a new low level. Hence one implication of a telomere homeostasis system is that any inhibitor of telomerase used in a therapeutic setting will likely have to be very potent.

Mutations made by others and by our group in Rap1p yeasts provide clear evidence for a role for Rap1p in telomere length regulation along the lines described in Fig. 5 (25–27). Here I outline data showing that, in addition, it is the telomeric repeat complex at the very end of the telomere — i.e., the complex assembled onto the very most distal repeats of the telomere — that is particularly crucial for telomere regulation. This is true even in the presence of a full-length, normal complex of internal wild-type repeats. As I will describe, even very small changes at the very ends of telomeres can cause loss of regulation of telomeres and loss of the capability of telomeres to cap chromosomes. Various experiments all converge on this same conclusion.

First, in the *K. lactis* system, which has the same Rap1 binding site and length regulation system as in *S. cerevisiae*, we made mutations in the telomerase RNA template sequence that to varying degrees lowered the binding affinity of the resulting mutated telomeric DNA to Rap1. The loss of affinity measured *in vitro* correlated with the degree of loss of length control *in vivo* (24, 25). One example of such a mutation was the Acc mutation, a point mutation in the Rap1 binding site in the telomeric repeat that dropped the binding affinity by a couple of orders of magnitude. As soon as one or two Acc repeats were added to the ends of otherwise wild-type telomeres, length control was completely lost, and these telomeres became very long and also very deregulated (uncapped), being degraded as well as lengthened (Fig. 6). The point here is that the internal tract was wild-type (WT) and close to normal length. Thus, at the point when telomere length became deregulated, the bulk of the telomeric complex, with the exception of its very end, was normal.

In a slightly different experiment, we made a different template mutant (called the AA mutant) which by itself had a very small effect on Rap1 binding and telomere length. However, when that mutation was combined with a small mutation in the C-terminal domain of Rap1, only a few mutant repeats had to be added before telomeres rapidly became severely deregulated and degraded (25).

A third type of experiment involved template mutations outside the Rap1 consensus binding site. We checked that the Rap1 binding affinity *in vitro* of such a mutant repeat was normal (25). One example was a mutation that introduced a site for the restriction enzyme KpnI into the telomeric repeat (Bgl mutant). Telomeres in Bgl mutant cells remain well regulated for quite a long time (24). However, when most of the wild-type repeats in a telomere have been replaced by Bgl repeats, through the process of encroachment diagrammed in Fig. 4, quite suddenly there is a complete loss of length regulation. The cells show abnormal enlarged morphologies and a large percentage of them have a much higher than normal DNA content and evidence of missegregated DNA (29).

In all three cases — the Acc mutant, the AA-Rap1-delta C double mutants and the Bgl mutants — putting the wild-type telomerase RNA gene back into the cells restored telomere length regulation (Figs. 7 and 8). The telomeres often remained very long, but were now regulated

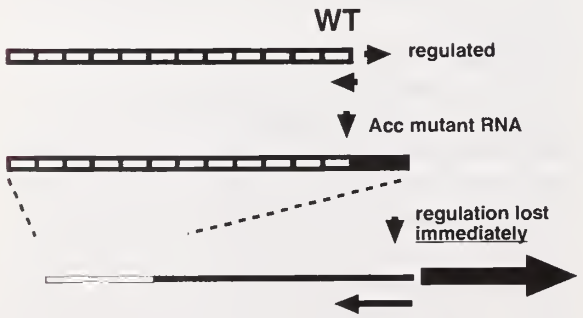

Fig. 6. Putting the wild-type (WT) telomerase RNA gene back into the cells restored telomere length regulation — the Acc mutant.

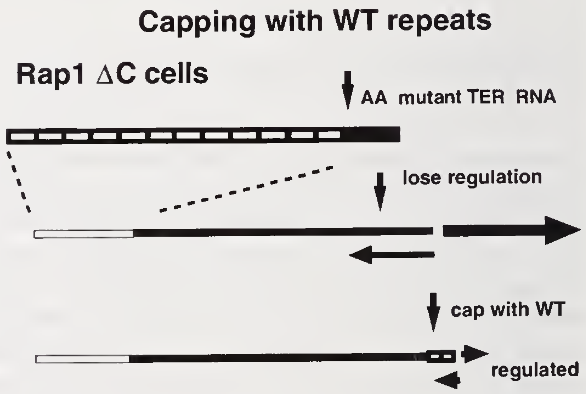

Fig. 7. Putting the wild-type (WT) telomerase RNA gene back into the cells restored telomere length regulation — the AA-Rap1-delta C double mutants.

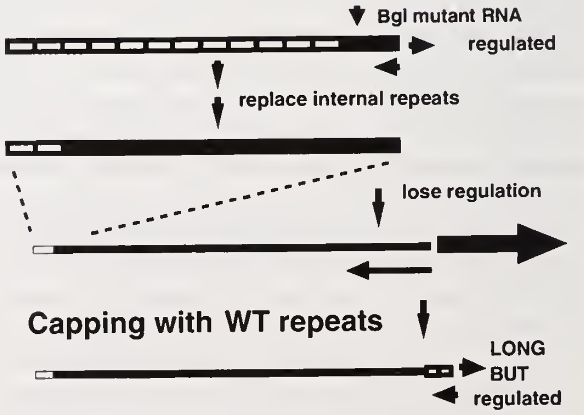

Fig. 8. Putting the wild-type (WT) telomerase RNA gene back into the cells restored telomere length regulation in the Bgl mutant cells.

tightly about their new, elongated lengths (25, 26, 29). Thus, we concluded that these telomeres had become functionally recapped. Interestingly, only a few initial type repeats were needed at the termini in order to restore capping.

The fourth experimental line of evidence came from work initially done in the ciliate *Tetrahymena*. We discovered that in the absence of proper capping function, telomeres fail to separate from each other in anaphase. This was shown when we made mutations in the template of the *Tetrahymena* telomerase RNA. Certain mutants prevented cells from completing anaphase (30). High resolution, 3-dimensional light microscopy indicated that the chromatids became stretched from one pole of the spindle to the other in anaphase, but their ends apparently failed to separate, so that they formed anaphase bridges at very high frequencies. Molecular analyses indicated that the tips of the telomeres in these mutant cells were comprised of mutant repeats, but the bulk of the telomeres were still wild-type (Fig. 9). Thus, this situation appears to resemble that in the Acc mutants in yeast, in which the ends of the telomeres were also mutant, leading to failure of DNA to segregate properly (29). Hence we speculate that, as in *Tetrahymena*, this failure results from the formation of anaphase bridges by fusion of the tips of uncapped telomeres.

In summary, telomeres and telomerase interact in cells to protect the ends of chromosomes and hence the genetic material of a cell. The telomerase RNP complex, which in at least yeast (and probably in other organisms) is oligomeric or dimeric, acts itself as part of the protective cap of telomeres that would otherwise be too short to be stable. In addition, the molecular nature of the very tip of the telomere is a crucially important determinant of whether the telomere can carry out the various functions that, in aggregate, we call capping.

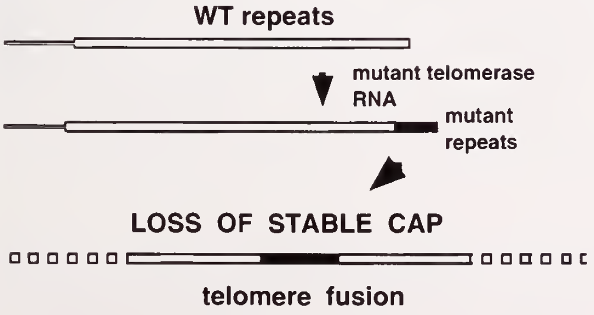

Fig. 9. The tips of the telomeres in the mutant cells were comprised of mutant repeats.

Acknowledgments

I gratefully acknowledge the colleagues in my laboratory who contributed to the experiments described in this article: I particularly thank Karen Kirk, Anamitra Bhattacharyya, Dave Gilley, Catherine Strahl, and He Wang, who have worked with *Tetrahymena* telomeres and telomerase, and Anat Krauskopf, John Prescott, Jagoree Roy, Tracy Boswell Fulton, and Chris Smith, who all worked on yeast telomeres and telomerases. I thank He Wang and John Prescott for providing Figs. 1 and 2 of this article. Research from the author's laboratory, as described in this article, was funded by grants GM26259 and DE11356 from the National Institutes of Health.

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Medical Education Grand Rounds

Scott H. Barnett, M.D., and Alex Stagnaro-Green, M.D.

Abstract

The primary goal of Medical Education Grand Rounds is to enhance the overall educational mission of the Mount Sinai School of Medicine. This editorial describes the first four years of this unique and innovative educational program, and serves as a prelude to a new feature of *The Journal*. **Key Words:** Medical education, grand rounds.

Introduction

The Mount Sinai School of Medicine inaugurated its Medical Education Grand Rounds series in September 1994. The goals of the series, as described in a preliminary description presented in 1995 in *Academic Medicine* (1), are to provide a forum for the dissemination of information about innovative educational programs and to allow an exchange of ideas that will enhance the overall educational mission of the institution. In this article, we wish to describe the first four years of the series and its impact on the institution.

Description

Medical Education Grand Rounds is presented weekly. A total of 95 lectures have been presented during its first four years. The speakers have been relatively evenly divided between faculty at the Mount Sinai School of Medicine (57%) and faculty invited from outside the institution (43%). The outside speakers, from all parts of the country, have been individuals with expertise in a broad range of medical education topics.

Grand Rounds topics can be divided into eleven broad categories (Table). A rich variety of topics have been presented in each. The largest category consists of presentations detailing innovative basic and clinical science curricula. Topics in the category of education theory and practice include evidence-based medicine, professional behavior, clinical decision making and problem solving, the medical interview, and research

TABLE
Medical Education Grand Rounds Topics

Category	# Presentations	% Outside Speakers
Course/clerkship curricula	18	33
Educational theory and practice	11	46
Curricular change/ reforms	10	80
Evaluation of student performance	9	44
Underrepresented minority/multicultural issues	9	44
Faculty issues	8	75
Computers/informatics	7	55
Graduate medical education	6	0
Ethics	4	50
Career choices	3	0
Miscellaneous	11	27
Total	95	43

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methods. Descriptions of curricular reform at other institutions have been a focus for our series. Student performance presentations covered changes in the United States Medical Licensing Examination (USMLE), peer evaluation, effective feedback strategies, and the use of "standardized patients," rigorously trained actors who first portray patients and then evaluate student's history taking, physical examination and interpersonal skills. Discussions of minorities and health care, multicultural diversity, disadvantaged students and women's issues formed another large category. Faculty topics included faculty development, teaching portfolios, and evaluation of faculty teaching skills. Miscellaneous topics included medicine and law, medicine and society, and dental and Ph.D. education.

Evaluation

We have attempted to evaluate the series in two ways. First, attendees rate the content of each presentation, the speaker's ability to convey information, and the usefulness of the material. Also, all outside faculty who present are sent evaluations to complete regarding their experience. Thus far, 63% of the speakers have responded to the mailings. Over three-quarters of the responders felt that Grand Rounds are very good or excellent forums for delivering their educational message and exchanging ideas. The facilities and audiovisual services were similarly well rated. We are gratified that several of the speakers commented that their experience has motivated them to explore creation of a similar series at their institutions.

Discussion

We believe that our Medical Education Grand Rounds, the first weekly education rounds in an American medical school, has achieved its stated goals. The series has served several important functions at the Mount Sinai School of Medicine. In its first year, it served as a forum where medical educators from all disciplines within the school could get to know each other; it continues to serve this purpose for faculty members new to the institution. In addition, the series has become a central focus for the exchange of ideas on curriculum and medical education within the school. As we move forward with a curriculum reform process, Grand Rounds function as a forum for discussion and debate. Furthermore, through the involvement of outside speakers, we have benefited greatly from the experience and expertise of many other institutions, and as such, have developed a national perspective on trends in medical education. As would be expected, it also has been helpful in developing a strong network of contacts nationwide.

In conclusion, our medical education Grand Rounds series has lived up to, and in fact surpassed, our expectations. We believe the series has served to influence our faculty. Moreover, the willingness of the outside speakers to be involved has impressed us. We strongly encourage other medical schools to develop similar programs.

To present some of the benefits of our Grand Rounds to a wider audience, we wish to introduce a new feature of *The Journal*. We will publish, from time to time, important topics that have been presented at the Medical Education Grand Rounds. We hope that the rigorous presentations will be informative to our readers and stimulate a lively discourse. We welcome your comments and suggestions.

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Emergency Medicine at the Mount Sinai School of Medicine

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Abstract

Emergency medicine became the twenty-third specialty by the American Board of Medical Examiners in 1979. Emergency physicians are specialists in the stabilization and resuscitation of medical and surgical emergencies in patients of all ages; they are experts in triage and in prioritization of resources. Emergency physicians provide the "safety net" for the American health care system, and they are the facilitators between the community and health care systems, and between primary care physicians and specialists. The emergency department is an ideal environment in which to teach the assessment and management of patients presenting with undifferentiated processes. Emergency physicians possess a unique set of clinical and research skills that have made them valuable members of the medical school academic community. Presented is a historical perspective on the specialty of emergency medicine and its evolving role at the Mount Sinai School of Medicine. Included are discussions on innovations in teaching developed by the emergency medicine faculty, including applications of computer-assisted instruction and the Internet. **Key Words:** Emergency medicine, undergraduate medical education, curricula, informatics, computer-assisted instruction.

Introduction

Over the past 25 years, emergency medicine (EM) has emerged as a recognized specialty by the American Board of Medical Specialties and as an important component of the medical school academic community (1, 2). EM has clinical, research, and administrative roles in the health care system that are unique to the specialty (3). It organizes and monitors emergency care delivery by coordinating emergency medical services (EMS) and hospital resources. At a societal level, EM is the safety net ensuring essential medical care 24 hours a day to all individuals regardless of their resources (4).

In 1994, the Josiah Macy Foundation sponsored a multi-disciplinary conference entitled "The Role of Emergency Medicine in the Future of American Medical Care" (5). The panel concluded that:

1) The federal government should establish as a goal "access to high-quality emergency medical care . . . for all persons who need such care."

2) Emergency departments (EDs) be classified according to the level of care available and that EDs advise patients of the qualifications and credentials of the attending physicians; the panelists were strongly critical of those EDs that were staffed by moonlighting, non-EM trained physicians.

3) The financing for EM postgraduate training be maintained in an effort to protect EM from the proposed funding cuts aimed at the non-primary care specialties.

4) "State medical licensing boards, the National Board of Medical Examiners, the Liaison

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Committee on Medical Education (LCME), and medical school deans and faculties must ensure that every medical student has acquired the appropriate knowledge and skills to care for emergency patients. This education must be provided through educational experience supervised by appropriately qualified emergency physicians."

5) "The deans and faculty of all LCME accredited medical schools . . . should establish in their schools appropriately staffed and supported academic departments of emergency medicine."

6) The American College of Emergency Physicians (ACEP) and the Society for Academic Emergency Medicine (SAEM) should convene a conference designed to establish the research agenda for the specialty and develop strategies to implement that agenda. That research conference was held in 1995 and the proceedings were published in 1998 (6).

Much progress has been made toward meeting these goals. This presentation will describe the evolution of Emergency Medicine, the discipline and its graduate training programs, and our institution's comprehensive undergraduate educational program designed to meet the above challenges.

The Field of Emergency Medicine

Emergency physicians are specialists in evaluating patients of all ages with undifferentiated medical conditions. Foremost, they are specialists in the stabilization and resuscitation of patients with both medical and surgical emergencies. They are experts in triage and in prioritization of resources, and are facilitators between primary care physicians and specialists.

The emergency department is an ideal setting to teach rapid patient assessment, stabilization, and differential diagnosis. It provides a provocative interface between the community and the health care system, routinely confronting students and care providers with difficult societal issues. Advanced directives, patient autonomy, child and elderly abuse, abandonment and suicide are only a few of the many issues that must be addressed, often simultaneously, on a regular basis in the ED. Consequently, in order to be effective, the emergency physician must be a patient advocate with strong clinical, communication, and administrative skills. The ED is a source of many patients with varying types and severities of illness for clinical research, and it offers a window on the community for epidemiologic and outcomes research. All of the above makes EM unique in its scope of practice and has earned it a critical role in medical education and research.

Historical Perspective

The first EM training program was established in 1969 at the University of Cincinnati (7). Until that time, there were no trained teachers of emergency medicine, nor was there a certifying board or specialty society. EDs were staffed by an assortment of clinicians from various backgrounds, who were frequently moonlighting and rarely had a commitment to providing comprehensive emergency care. In academic centers, the ED was usually staffed by house officers with limited faculty supervision, leaving the sickest patients to be seen by the least experienced physicians.

By 1975, there were 10 residency programs in the United States. In 1979, the American Board of Medical Specialists (ABMS) created the American Board of Emergency Medicine (ABEM), making it the twenty-third recognized medical specialty (2). In that same year, the Federal government allocated funding for graduate EM residency training and in 1980, the Residency Review Committee (RRC) for Emergency Medicine was established through the Accreditation Council for Graduate Medical Education (ACGME).

The intent of ABMS certification is to ensure that a practicing physician has completed an accredited educational program and has demonstrated competency in providing quality patient care. Learning from other specialties, ABEM created a practice tract that accommodated those physicians working in EDs prior to the creation of a sufficient number of residency training programs. The first ABEM examination was given in 1980. The last year non-EM residency trained applicants could apply to the board was 1990. The ABEM exam has a one-day written component and a one-day oral component, and certification is valid for 10 years. In 1998, there were 15,898 physicians certified by ABEM, with an estimated 25,000 full-time equivalent positions available in the specialty (8).

Emergency Medicine Residency Training

In 1997, there were 3,239 residents-in-training in the 119 RRC-accredited EM residencies; 72% of these trainees were male and 27% female (7). ABEM requires a minimum of 36 months of training in an ACGME-accredited EM program, although many educators believe that 4 years is the minimum time required to effectively teach all of the competencies needed in the specialty of EM.

The curriculum core content for EM training covers medical and surgical disorders in patients irrespective of age (9). In addition to issues in medical and traumatic resuscitation, the curriculum emphasizes administrative topics such as accreditation, reimbursement, personnel management, wellness, and interdepartmental relations. EMS and disaster medicine are strongly represented in the curriculum since pre-hospital care has a prominent interface with the ED care.

Emergency Medicine in Undergraduate Medical Education

One of the goals in medical education is teaching students how to assess the cardiopulmonary status of a patient (the "ABCs"), and to provide life-saving interventions when indicated. The thought of a student finishing medical school without knowing the fundamentals of resuscitation and of basic first aid seems incomprehensible and contrary to the precepts of medical education as defined by the LCME (10). A survey performed in 1994 showed that approximately 70% of medical schools did not require basic first aid in their curriculum, approximately 60% did not require advanced cardiac life support skills, and 20% did not require basic cardiac life support skills (1). Approximately 90% of schools surveyed did not require Advanced Trauma Life Support (ATLS) skills. The same survey revealed that only 20% of medical schools had a required clerkship in EM.

Clearly, there are many opportunities throughout the clinical years for medical students to be exposed to acutely ill or injured patients. The creation of a formal curriculum designed to ensure a minimum exposure to EM concepts is desirable, and has become more easily attainable with the growing presence of EM academicians. In 1996, there were 124 LCME-accredited medical schools, of which 41% had recognized academic departments of EM, a 23% increase over the number in 1991 (11).

Several publications have dealt with curriculum design for emergency medicine in undergraduate education (12, 13). In 1990, the SAEM Education Committee published a 4-year curriculum that was modified in 1998. The curriculum presents goals and objectives, and links them to teaching methods. It focuses on 3 core content areas: acquisition of basic life support skills, including the diagnosis and treatment of shock; the differentiation and treatment of common acute problems; and the assessment of the undifferentiated patient (14).

The Department of Emergency Medicine at the Mount Sinai School of Medicine has worked from the models developed by ACEP and SAEM, and has developed a comprehensive EM experience for the medical students. The following sections in this paper present the mandatory first and fourth year EM experiences, the various elective opportunities that are available, and some of the innovations that have been implemented to facilitate didactic and bedside learning.

The First-Year Curriculum

From the first day of medical school, students sense the need to have a working knowledge of fundamental health care concepts. While it is acceptable for a student to plead ignorance on a complicated medical question, it is far more difficult to justify ignorance in the case of basic first aid and emergency care.

The EM experience for first-year students at the Mount Sinai School of Medicine is taught during the first three weeks of the academic year and is designed to provide the basic principles of patient assessment and stabilization. The course uses case studies, small group teaching, and problem-based learning (PBL) techniques to teach the knowledge, skills, and attitudes needed to assess victims of illnesses or accidents, and provides the students with skills to function as a first responder (Tables 1 and 2). It also includes 8 hours of Basic Life Support (BLS) taught by third- and fourth-year medical student American Heart certified instructors.

Students are taught how to recognize emergencies and to prioritize care. The emphasis is on the use of everyday materials in stabilization and treatment. Students are taught the importance of identifying clues in the environment that may be helpful in managing the patient with an undifferentiated problem. Cardiopulmonary resuscitation and managing an obstructed airway for both adult and pediatric patients are considered an integral part of the curriculum. This not only prepares the student for clinical rotations, but gives the student a potentially lifesaving skill.

The course also introduces students to history taking and physical exam skills. Behavioral and human interest issues are stressed, such as the various presentations of substance abuse, as well as elder and child abuse. Ethics issues, which frame how we deal with the complexities of medicine, societal issues and our own personal beliefs, are woven throughout the discussions.

TABLE 1
First-Year Curriculum

Introductory Lecture and Approach to the Patient in the Field	2 hours
Medical Emergencies	
Shortness of Breath, Chest Pain, Allergic Reactions	2 hours
Change of Mental Status, Hypo/ Hyperglycemia, Poisoning and Overdose, Seizures	2 hours
Environmental, Travel and Behavioral Emergencies	2 hours
Trauma	
Central Nervous System Trauma, Immobilization, Musculoskeletal Trauma	2 hours
Truncal Trauma, Burns and Cold Injuries	2 hours
Pediatric and Obstetrical Emergencies and Out-of-Hospital-Childbirth	2 hours

TABLE 2
Skills Taught in the Small Group Sessions in the First-Year Course

BLS(1): CPR(2) and obstructed airway
Airway and breathing assessments
Pulse evaluations
- Location
- Presence
- Strength
- Rate
- Rhythm

Controlling hemorrhage and epistaxis
Cervical spine immobilization
Extrication
Logrolling(3), extrication and transport
Bandaging and splinting
Automatic external defibrillator use

(1) BLS = basic life support
(2) CPR = cardiopulmonary resuscitation
(3) Logrolling = turning the patient while maintaining spinal immobilization

Psychomotor skills such as applying and maintaining cervical spine immobilization, assessing the patient's airway, breathing, and circulation are emphasized. Slides and videotapes are augmented by demonstrative materials such as epinephrine autoinjector pens, rudimentary splinting materials, nitroglycerin bottles, and automatic external defibrillators. Attendance is mandatory and active participation is encouraged.

Successful completion of the course requires passing the written BLS exam, the practical BLS exam, and a PBL practicum which consists of a case scenario that requires an integration of the primary concepts taught in the course. The case consists of an accident involving patients with a variety of medical and surgical problems. Students must identify the problems, prioritize care, render stabilization, and make disposition decisions. Groups of 5 students have 5 days to work together to formulate a response. A composite essay written by the group is handed in for evaluation; students have the option of meeting with course faculty to review their performance in depth.

Evaluations of the course have been quite positive. Of the 90 students who have completed the clerkship, 90% submitted an evaluation. Approximately 82% responded that the course strongly stressed problem solving; on the quality of the course, 80% rated it either "Excellent" or "Very Good."

The Shadow Program

The shadow program, or pre-clinical Emergency Medicine, is designed to offer exposure of first- and second-year students to human pathology and socioeconomic problems concurrent with didactic education. The program began in 1996 as a single student's request for a four-hour period of observing clinical practice, and has evolved into weekly sessions which include not only observing, but also assisting attending physicians and nurses with limited patient care activities. Student responsibilities include identifying new words or concepts relevant to the day's patients, and reporting back the following week on what was discovered regarding the word or concept, thus incorporating problem-based learning into the program. During the 1998 academic semester, there were 20 requests for the 8 available positions. Driven by demand, the shadow program has been expanded to 12 students.

The Fourth-Year Curriculum

Beginning in the 1997–1998 academic year, EM became a required fourth-year clerkship at the Mount Sinai School of Medicine. The three-week rotation provides a mixture of didactic and hands-on patient care. It is designed to give students an opportunity to approach undifferentiated clinical conditions, and to interface with pre-hospital care providers, hospital administrators, and in-house consultant services. In essence, students function as "subinterns" at one of three clinical sites. Students are expected to complete 10 twelve-hour shifts during which they see between 4 and 8 patients, depending on the numbers of patients and the severity of their illnesses. Students see patients according to their triage category and they are thus introduced to the concept of prioritizing care. Once patients have been examined, students are expected to generate a differential diagnosis and a management plan. Cases are presented directly to an ED attending physician who then helps guide the student through the patient care plan. Attending physicians are assigned only one student per day, thus allowing time for an intimate interaction including bedside teaching.

Complimentary to the clinical experience, students are provided with 9 hours of standardized, case-based lectures, a one-hour ethics conference, a four-hour suture and splinting laboratory, and a volume of core reading material from the peer-reviewed literature. The lectures are given in 3 three-hour blocks, and cover the approach to altered mental status, poisoning and drug overdose, weakness and dizziness, headache, asthma, abdominal pain, chest pain, arrhythmias, and trauma. The case-based scenarios emphasize triage, prioritization, stabilization, and recognition of life-threatening process. These same cases, as well as additional material, are presented on the Internet in the form of computer-assisted instruction, therefore allowing students 24-hour access to course materials (see CyberSchool section below).

The suture lab includes a didactic presentation on wound preparation and aftercare; it is followed by a hands-on demonstration and practicum using pigs' feet or chicken thighs. Splinting skills are practiced on each other with the assistance of faculty and EM residents. An optional live swine laboratory is also offered where students are taught central line placement, tube thoracostomy, venous cut down, cricothyroidotomy and peritoneal lavage techniques.

In addition, students are exposed to the business foundations of medical practice and the organization, structure, and functions of the public and private health care funding organizations. It is intended that our students learn basic information that will ultimately be needed to negotiate with these agencies to further the care of their own patients while legitimately supporting their future clinical practices.

Students' grades are based on shift evaluations, a 50-question multiple choice written exam followed by an oral discussion of the answers, participation in a conference, and a review of the log books. The shift evaluation forms review and evaluate the student, based on number of patients seen, supervision of procedures, history-taking and physical exam skills, ability to formulate differential diagnosis and formulate management plan, ability to interpret laboratory tests, technical ability, ability to interact with patients, oral presentations and comments. The evaluations are given back to the student at the end of each shift, providing them with timely, ongoing feedback on their performance and facilitating the teacher/student relationship. Student log books capture the name, unit number, telephone number, presenting complaint, discharge diagnosis, important clinical and laboratory findings, procedures and, most important of all, follow-up of the patient after discharge from the ED. The purpose of the log book is to help the student track their clinical experience, and to ensure that depth is given to experience by obtaining outcome information on their patients. Log books are reviewed for their completeness, and during the last lecture day, students are asked to present an interesting case that they followed up on.

Computer-Assisted Instruction: The CyberSchool

The use of computer-assisted instruction (CAI) in medical education has emerged as a valuable tool to educate "on demand." This is especially useful in sites such as the ED where patient flow is 24 hours a day and unpredictable. Its use has rapidly increased over the past 20 years and has been the topic of numerous publications and journals including the *Journal of Education Computing Research* and the *Journal of Computer-Based Instruction* (15, 16). There is some evidence, including a recent meta-analysis of 120 studies (15), that suggests CAI is superior to traditional forms of teaching. CAI has also been shown to reduce the amount of time it takes to learn an objective, and to improve post-test scores from the 50th to the 60th percentile (16, 17). In 1992, a panel convened by the Association of American Medical Colleges (AAMC) recommended that medical schools should lead in the application of information science and computer technology and promote their effective use (18, 19). The AAMC directory now shows that virtually all medical schools employ computers in some aspect of medical education. Medical students desire greater use of computers in their education (20), and leading medical educators believe that ". . . a strong grounding in the use of computer technology to manage information, support patient care decisions, select treatments, and develop their abilities as lifelong learners. . ." is essential for medical students (21). Recent literature in *Academic Medicine* debated the value of requiring all medical students to own their own computers as well as the need for enhancing faculties' competencies in programming and using computer-aided tools (22, 23).

As emergency medicine becomes an accepted part of undergraduate medical education, it is important to explore how best to teach students without taking time away from patient care. Toward this end, the Department of EM at the Mount Sinai School of Medicine developed its CyberSchool (http://mssm.edu/emergmed), an interactive CAI program designed to assist teaching and learning via the Internet. It helps students acquire resources and skills that encourage them to become effective lifelong learners.

CyberSchool combines two powerful entities: the Internet and CAI. New hypertext and multimedia technology (HTML), as well as the wide acceptance of the Internet, enhances the efficacy of CAI. The World Wide Web allows users to receive a graphic representation of data and point-and-click to more information. Data can be accessed any place, any time, as long as a computer with a proper modem is available. Reproducible visual stimuli can be turned into graphic images; rashes, wounds, and physical findings, as well as x-rays, CT scans, MRIs, and ultrasound (even in real time), can all be presented using this technology. More important, a lecture, review, or case conference does not have to be missed simply because a student is tired after working an overnight shift. Lessons can be given right in the ED during lulls in patient volume. The same presentation can also be given simultaneously at different sites, without having to coordinate transportation of individuals to a single location.

CyberSchool consists of 3 educational components: EM Case Conference, Photoland, and Interesting Case of the Week.

1) **EM Case Conference:** A case-based interactive tool that includes 8 modules: Advanced Cardiac Life Support (ACLS) review, Ear-Nose-Throat (ENT), toxicology, trauma, environmental emergencies, Obstetrics/Gynecol-ogy, ophthalmology, and orthopedics. Each module contains 3 – 5 cases which illustrate the presentation and management of common EM problems.

2) **Photoland:** Each photograph has a mini-case presentation and asks sample questions for group discussion. It is followed by a mini review of didactic material. The photographs are obtained using digital images photographed in the Mount Sinai ED, with written patient consent.

3) **Interesting Case of the Week (I.C.O.W.):** This feature, currently being beta tested, will be a case-based interactive tool that presents an actual patient seen in the ED. It allows the user to determine a differential diagnosis and attempt to manage the patient. A new case will be presented each week, including pertinent patient photos, x-rays, ECGs or sonograms. This tool will allow individuals who are unfamiliar with HTML to put their cases into the necessary format to be put onto the website. Thus, the use of CAI by faculty to aid in their teaching duties will not be limited to individuals with specialized expertise in HTML programming.

In conjunction with the development of the CyberSchool, a research protocol has been established to study its impact on the education of Mount Sinai medical students. Supported by an "Innovation in Medical Education Grant" from the Emergency Medicine Foundation, the accessibility and impact of this CAI educational tool is being studied. Half of the Mount Sinai students have access to the CyberSchool during their EM rotation while the other half do not. Preliminary data suggests that 73% (36/49) of students are in favor of CAI as an adjunct to their EM curriculum. The number of a student who had access and who actually used the educational tool was 36% (9/25). The data on whether or not the users performed better on the final examination, and whether they were more satisfied with their EM educational experience, is still being collected and analyzed.

The Future of EM at the Mount Sinai School of Medicine

The Mount Sinai School of Medicine is in the final stages of a complete review and redesign of the undergraduate curriculum. A new curriculum will be introduced beginning with the Class of 2004. Important features include integrated, non-department-based courses, early introduction of clinical experiences, increased use of small-group teaching, and the effort to foster lifelong learning and evidence-based practice skills.

The undergraduate curriculum in EM can help meet these goals from several perspectives. During the EM clerkship, students will be exposed to a large number of new patients with a broad range of presenting problems and chief complaints. The EM curriculum will be designed to assist students in making sound decisions by applying evidence-based information relating to patient diagnosis, management, and prognosis. In addition, because the ED's scope of practice is so broad, the curriculum can help students review the basic mechanisms of disease, normal physiology, and pathophysiology for a large number of disease entities and presentations.

In the future, we expect that much more sophistication will be required in information management and technologies. To prepare Mount Sinai graduates, the ED curriculum will present selected topics in medical informatics and database management. This process has already begun with the creation of the Department of Emergency Medicine's CyberSchool website. In the future, elements used in the CyberSchool will be presented by a consortium of educators drawn from a number of departments, in addition to Emergency Medicine.

We believe that bedside technologies will continue to expand and that there will be diagnostic modalities available at the bedside which will render the stethoscope almost obsolete. These modalities will include imaging techniques, as well as very sophisticated, inexpensive point-of-care testing equipment. The current practice that requires most patients to schedule testing, obtain the tests, and then return for test results and follow-up will be a foreign concept. "One-stop shopping" will be the rule. If a patient requires a consultation, it may be performed on-line via a telemedicine hook-up, thus saving the patient and the consultant time and money. Our students will need the training and practice in the use of these clinical modalities, and the ED will be in the forefront of this technological revolution.

Finally, we hope to change the focus of our practice from one which not only responds to intercurrent emergencies and urgencies, but one that also focuses on elements of preventive medicine. Thus, the curriculum will encompass a review and overview of the preventive measures that have been shown in an evidence-based fashion to be important, and strive to incorporate these measures into our practice patterns whenever it is appropriate. This focus will continue to blur the sharp demarcation of functions and services that are provided in an ED and those provided in primary care settings. Since EDs are always open and have periods of reduced traffic, the provision of preventive health services in the Emergency Department will be a cost-effective and convenient vehicle to maximize public health. Our trainees will have these elements of preventive health care both discussed and illustrated during their rotations through our department.

At this juncture, the future looks very bright, busy, challenging, and exciting for both faculty and students. For students rotating through emergency medical programs, the quality of their professional lives and their ability to offer their patients and families exemplary care will be supported and enhanced by a curriculum that will anticipate their needs and the needs of their patient as we begin the twenty-first century.

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Selective Decontamination of the Digestive Tract Helps Prevent Bacterial Infections in the Early Postoperative Period after Liver Transplant

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Abstract

In liver transplant (LTx) recipients, gut-associated bacterial and fungal organisms produce significant postoperative morbidity and mortality. We sought to assess the role of selective digestive decontamination (SDD) in preventing postoperative infections in a large single-center cohort of liver recipients transplanted under two non-simultaneous protocols. In 212 consecutive patients transplanted between 1/1/91 and 7/31/92, SDD (gentamicin 80 mg, polymyxin B 100 mg, nystatin suspension 10 mL) was employed, starting after induction of anesthesia and continued until POD 21 (SDD Group). In 157 consecutive patients transplanted between 1/1/93 and 12/31/93, SDD was not used (non-SDD Group). Both groups received IV vancomycin and cefotaxime prophylaxis. All culture-positive infections within the first 30 days post-LTx were recorded and classified as bacterial or fungal. Infection-related mortality (patients who died of infectious complications without any technical complication) was recorded. Groups did not differ in patient demographics, United Network for Organ Sharing (UNOS) status, use of veno-venous bypass, total/warm ischemia, or length of ICU stay. Infections developed in fewer SDD patients (56/212; 26%) than non-SDD patients (69/157; 44%) ($p<0.001$). The incidence of gram-negative infection was less in the SDD group (11% vs. 26%, $p<0.001$) as was gram-positive infection (16% vs. 26%, $p<0.001$). Among patients who developed infection, there was no difference between groups in infections per patient. Primary graft non-function (PNF) developed in 20 SDD patients (7/20 had infections) and 8 non-SDD patients (6/8 had infections) ($p=0.06$). There were no differences in incidence of fungal infections or of infection-related mortality between groups. In the SDD group, there were fewer abdominal ($p<0.001$), lung ($p<0.001$), wound ($p<0.01$), and urinary tract infections ($p<0.05$).
Conclusion: Use of SDD in liver recipients early after transplant was associated with significantly fewer infections in the early postoperative period. **Key Words:** Liver transplantation, selective digestive decontamination, postoperative infection, infection prophylaxis.

Introduction

Liver transplantation (LTx) is the only therapeutic modality for patients with end-stage liver disease, with one-year survival of 85% (1). Increased experience with candidate selection, refinement of surgical technique, and advances in immunosuppression and organ preservation contribute to successful outcomes. On the other hand, postoperative infectious complications still remain an important cause of morbidity and mortality. The reported incidence of severe infections after LTx ranges from 53% to 79% (2–3). Endogenous gut-associated bacterial and fungal organisms are the most frequently encountered pathogens (4, 5). Approximately three quarters of bacterial and fungal infections occur in the first month following LTx (4, 6).

Early in our program, between January 1991 and July 1992, selective decontamination of the digestive tract (SDD) was employed routinely. Near the end of this period, we began to see an increasing number of vancomycin-resistant *Enterococcus faecium* infections, and the decision was made to abandon SDD prophylaxis.

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Between January 1993 and December 1993, SDD was not used at all. Because there have been no large studies to evaluate the role of SDD in preventing early postoperative infection in liver allograft recipients, we undertook a retrospective analysis of these two protocols (SDD and non-SDD) to assess whether SDD prevented or decreased the incidence of postoperative infection.

Patients and Methods

A total of 369 liver recipients underwent LTx under these two protocols (SDD vs. non-SDD). Between 1/1/91 and 7/31/92, 212 consecutive patients underwent LTx with use of SDD (SDD group). Between 1/1/93 and 12/31/93, 157 consecutive recipients received no SDD (non-SDD group).

Liver transplantation was performed as described previously (7). Induction immunosuppression was cyclosporine (CsA)-based (CsA, steroid, azathioprine) or FK506-based (FK506 and steroid); OKT3 was used in patients who had had renal failure prior to LTx.

The SDD suspension was a mixture of gentamicin, 80 mg; polymyxin B, 100 mg; and nystatin, 2 million units per 10 mL dose. Patients received 10 mL of SDD suspension every 6 hrs, starting after induction of anesthesia, until postoperative day 21 (mechanical bowel preparation was not routinely employed). The SDD suspension was given by nasogastric tube while the patients were intubated, and by mouth after extubation. In addition, a paste (compounded in the hospital pharmacy) consisting of gentamicin 2%, polymyxin-B 2%, and nystatin 100,000 units/gram in Orabase® (Colgate Oral, Canton, MA) was applied to the oral mucosa every 6 hrs during the period of postoperative endotracheal intubation.

All patients in both groups received 48 hr prophylaxis with IV vancomycin, 1 g every 12 hrs, and cefotaxime, 1 g every 8 hrs.

The following variables were recorded and compared: (1) patient demographics; (2) pretransplant United Network for Organ Sharing (UNOS) status; (3) primary disease; (4) incidence of pretransplant spontaneous bacterial peritonitis (SBP); (5) intraoperative use of veno-venous bypass (i.e., bypass circuit used during the anhepatic phase to carry venous blood from lower torso and portal circulation into the heart through the axillary vein); (6) warm and total ischemia times (i.e., interval from cross-clamping of the aorta in the donor to reperfusion in the recipient [total ischemic time]; and interval during which harvested organ is not cold-preserved [warm ischemic time]); (7) total operative time; (8) intraoperative blood use; (9) technique of bile duct reconstruction; (10) occurrence of primary graft non-function (PNF); (11) induction immunosuppression regimen; (12) length of ICU stay; and (13) cost of SDD.

All culture-positive infections during the first 30 days post-LTx were recorded and classified as bacterial (gram-positive or gram-negative) or fungal. The number of methicillin-resistant *Staphylococcus aureus* (MRSA) infections and vancomycin-resistant *E. faecium* (VREF) infections were also recorded in each group. Definitions of infections appear in Table 1. Infection-related mortality (i.e., death related to infectious complications without any technical complication) was recorded as well.

Chi square, T test, and Mantel-Haenszel test were used for statistical analysis. $P<0.05$ was considered significant.

Results

In the SDD group, 212 recipients underwent 237 LTx; 24 recipients received more than one LTx (23 patients had 2, 1 patient had 3 liver transplants). In the non-SDD group, 177 LTx were performed in 157 patients; 15 recipients received more than one LTx (11 had 2, 3 had 3, and 1 patient had 4 transplants). There was significant no difference between groups in primary disease (Table 2), patient demographics, UNOS status at transplant, or SBP. Groups were also similar in warm ischemia, total ischemia, total operative time, intraoperative blood use, technique of bile duct reconstruction, occurrence of PNF, and ICU stay (Table 3). In the SDD group, veno-venous bypass was used more frequently than in the non-SDD group ($p<0.001$). As outlined in Table 4, infection rates for bypass and non-bypass patients

TABLE 1

Definitions for the Diagnosis of Clinical Infection

Clinical signs of infection
Pyrexia > 38.5°C
WBC > 15,000
Culture of organism within 72 hours
Lung infection
New infiltrate with clinical signs
Culture of organisms from sputum
Wound infection
Redness/induration and the presence of pus on exploration
Positive wound culture
Sepsis
Clinical signs with a positive blood culture
Urinary tract infection (105 cfu/hpf)

TABLE 2

Indication for Liver Transplantation

	SDD* n=212	Non-SDD* n=157
Alcoholic	39	18
Autoimmune	9	9
Biliary atresia	12	9
Cryptogenic	18	16
Fulminant hepatitis	16	11
Viral hepatitis	58	56
Cholestatic	48	27
Others	12	11

* The differences between the two groups are not statistically significant.

TABLE 3

Patient Demographics, Operative and Postoperative Data

	SDD* n=212	Non-SDD* n=157
Age	43.9 (8 mos–71 yr)	45.2 (9 mos–70 yr)
UNOS 3-4	133	90
UNOS 1-2	104	87
SBP	6	8
Warm ischemia time (min)	52±10.3	50±11.4
Total ischemia time (hrs:min)	12:20±6:00	10:9±7:10
Total operative time (hrs:min)	9:00±5:34	7:20±4:50
Packed red blood cells (PRBC) (unit)	15.8±17.2	11±15.4
Fresh frozen plasma (FFP) (unit)	15.5±14.2	12±11.9
Bile duct anastomosis		
Duct-Duct	187	105
Roux-Y	50	52
Mean ICU stay (days)	4±12	4±14.5
PNF	20	9

* The differences in the two groups are not statistically significant.

TABLE 4

Bypass Status and Infection Rate

Bypass	Infection	SDD* n=210#	Non-SDD* n=157
Yes	Yes	49 (26.2%)	36 (51.4%)
	No	138 (73.8%)	34 (48.6%)
No	Yes	7 (30.4%)	33 (37.9%)
	No	16 (69.6%)	54 (62.1%)

# Data on two patients are missing.

* The differences between the two groups are not statistically significant.

TABLE 5

*Comparison of Incidence and Type of Infection Between Groups**

	SDD (n=212)	Non- SDD (n=157)	p value
Patients with infection	56 (26%)	69 (44%)	<0.001
Gram-negative	22 (11%)	38 (26%)	<0.001
Gram-positive	32 (16%)	41 (28%)	<0.01
Fungal	10 (5%)	11 (7%)	NS

* Some patients had more than 1 type of infection.

TABLE 6

*Site of Infection**

	SDD n=212	Non- SDD n=157	p value
Abdomen	11 (5%)	30 (19%)	<0.001
Lung	13 (6%)	28 (18%)	<0.001
Sepsis	17 (8%)	22 (14%)	0.06
Wound	23 (11%)	32 (20%)	< 0.01
UTI**	2 (1%)	7 (4%)	<0.05

* Some patients had more than 1 type and site of infection.

**UTI = urinary tract infection.

in both the SDD and non-SDD groups were essentially the same by Mantel-Haenszel test.

Bacterial infections developed in significantly fewer patients in the SDD group than in the non-SDD group (p<0.001) (Table 5). There was no difference in the incidence of fungal infections between groups. As shown in Table 6, in the SDD group there were fewer abdominal (p<0.001), lung (p<0.001), wound (p<0.01), and urinary tract infections (UTI) (p<0.05); there was no statistical difference between groups regarding sepsis. Between our two groups, there was no difference in the incidence of MRSA infection (14 cases in the SDD group vs. 11 cases in the non-SDD group). The incidence of VREF infections was significantly higher in the non-SDD group (19/157, vs. 11/212 cases in the SDD group, p=0.02). There were 7 infection-related deaths in the SDD group vs. 11 in the non-SDD group (p=ns).

For each treated patient, the daily cost of SDD was $7. The mean total cost per patient (for a 3-week course) was $161.

Discussion

Infectious complications following liver transplantation result in long-term hospitalization, especially in the ICU, and are the leading cause of morbidity and mortality. Responsible pathogens are usually intestinal in origin. In recent studies, up to 74% of bacterial and fungal infections occurred during the first 4 weeks after liver transplantation (4, 6). The concept of a reduction of gut-associated bacterial and fungal sepsis in liver recipients with use of SDD appears very appropriate.

Wiesner (8) has shown a reduction in the incidence of gram-negative and fungal sepsis after using SDD in liver transplant recipients, with SDD initiated from days to weeks prior to LTx and continued for 3 weeks post-LTx. We deemed this approach impractical, however, since waiting time in our patient population is always more than 5 months. Thus, we elected to start SDD immediately prior to surgery.

In our study, we found no difference in the incidence of fungal infections between groups. In a randomized prospective study of 36 pediatric liver recipients, Smith et al. (9) found significantly fewer gram-negative infections among patients who received SDD and no difference in gram-positive infections, but mortality was not significantly affected. In our patients, with the use of SDD, we were able to decrease the incidence of both gram-negative and gram-positive infections.

We could find no correlation between bypass use and infection rate. In our SDD group, infection rates for bypass and non-bypass patients were similar. In the non-SDD group, the bypass patients had a higher incidence of infection than those patients who did not have bypass, although the difference did not reach statistical significance. Whether or not the use of bypass in the non-SDD group promoted the occurrence of infectious complication is not amenable to further analysis in our study (10).

Miller et al. (7) have shown that SDD may cause an increase in the incidence of gram-positive infections, especially MRSA. Between our two groups of patients, there was no difference in the incidence of MRSA infection. However, SDD was associated with a significant reduction in the incidence of gram-positive infection in our study (16% vs. 28%, $p<0.01$).

In addition to the reduction in overall incidence of infection, SDD was associated in our study with a reduction in infections involving the abdomen, lung, wound, and urinary tract.

Unfortunately, our study suffers from a number of limitations common to most retrospective reviews. We did not perform routine surveillance cultures, nor did we control for pretransplant use of immunosuppressive drugs or prior abdominal surgery. However, patients in both groups were well matched for pretransplant risks, including diagnosis and UNOS status. In our series, the incidence of fungal infections in the SDD group (5%) and in the non-SDD group (7%) were lower than in other reported series (4, 5, 9). We have no explanation for this difference.

Although we abandoned our original SDD protocol because it was felt to be associated with an increasing number of VREF infections, our retrospective analysis showed us that SDD did not increase the incidence of VREF infection. In fact, the incidence of these infections was higher under the non-SDD protocol. One explanation for the occurrence of VREF infections in both groups could be our prophylactic use of vancomycin.

Based on these results, since January 1994 we have resumed the use of a modified SDD protocol in our recipient population. In this modified protocol, our SDD suspension and the oral paste remain unchanged, but the duration of administration of the SDD suspension is limited to 7 days, and vancomycin is no longer administered prophylactically. Results with our use of this newer protocol have yet to be published.

We conclude that use of SDD after liver transplantation resulted in a significant reduction in the incidence of infections. SDD did not, however, decrease the number of fungal infections, the length of ICU stay, or overall and infection-related mortality.

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Pig Organs for Transplantation into Humans:

A Jewish View

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Abstract

In view of the shortage of human organs for transplantation, intense interest has focused on the use of pig organs. Although the early rejection of pig organs by a human recipient has not yet been overcome, scientists are actively seeking to solve this problem. If and when xenotransplantation from pigs or other animals becomes scientifically feasible, Judaism will look with favor upon this procedure to prolong or save the life of a human being who is ill or dying from organ failure. Although Jewish law forbids Jews to raise or eat pigs, no such prohibition exists for the use of pigs to cure human illness or to save human lives by xenotransplantation. **Key Words:** Transplantation, pig organs, xenotransplantation, Judaism.

Introduction

The shortage of human organs for transplantation into patients suffering from organ failure has generated great interest in the use of animal organs as xenografts (1–4). For this purpose, organs from primates and pigs have received the most attention (5–6). The main reasons for the current lack of long-term success with xenografts are the immunological barriers to the acceptance of xenogeneic tissues (7–8), and the potential of transmitting both recognized zoonotic pathogens and unknown xenogeneic agents (9) by xenotransplantation. Recently, Paradis et al. reported that infection with porcine endogenous retrovirus (PERV) did not occur in any of 160 persons exposed to living pig tissue (10).

The rejection by the recipient of a xenograft is vigorous and often immediate, and is not adequately controlled by conventional immunosuppressive therapy used for allografts. The rejection is due to natural immunity by recipients never before exposed to xenografts, or to naturally occurring, pre-existing antibodies against the xenograft endothelium, or to activation of the alternative pathway of complement (11). However, progress is being made in understanding how removal and/or neutralization of these antibodies and the limitation of complement activation may be achieved (12).

Another promising approach is the use of organs from genetically engineered pigs, which do not stimulate the usual hyperacute rejection in the human recipient. Several routes are being explored to successfully breed such pigs (13), with the hope that doing so will provide an adequate supply of donor organs for clinical use.

People who observe the Jewish dietary laws (14–15) are forbidden to raise pigs or eat their meat. It might thus be argued that transplanting pig organs into observant Jews would be prohibited. This is not the case, however. Although Judaism prohibits the consumption of pork, it does not forbid deriving benefit from pork. Thus, for decades, the use by diabetics of insulin made from pork has been permissible in Jewish law, as is the use of porcine heart valves.

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Furthermore, Judaism is guided by the axioms of the supreme sanctity of human life and the dignity of man created in the image of God. The preservation of human life in Judaism is a divine commandment. To save a life, all religious laws are automatically suspended, the only exceptions being those forbidding idolatry, murder, and certain sexual relations such as incest or adultery (16). Thus, Judaism would certainly condone the transplantation of pig organs into Jewish recipients in order to save their lives.

There are other reasons why pig organ transplantation into humans is an important issue to address at this time. For a variety of medical, practical, ethical and financial reasons, most attention is being focused on the pig rather than on primates as the best donor of vascularized organs for human patients (17). It is available in large numbers; it is easy to breed and maintain; it is similar in anatomy and physiology to man; it is able to breed under pathogen-free conditions; and it is more likely to receive public acceptance than primates (13). With such a seemingly ideal source of organs, the prospects for the future of xenotransplantation are indeed promising and encouraging (18). This essay discusses some of the moral issues involved in xenotransplantation and presents a detailed exposition of the Jewish view on the use of animals, including the pig, in the service of mankind.

Ethical Issues in Xenotransplantation

The shortage of human cadaveric organs for transplantation is well recognized. In an effort to alleviate this shortage, better artificial organs are being more effectively and efficiently employed, along with the more frequent use of organs obtained from willing and suitable related and even unrelated living donors. However, each of these "solutions" is associated with a variety of practical, medical, and moral issues beyond the scope of this essay.

The use of animal organs as xenotransplants also raises a number of ethical issues. Is it moral to breed, raise and kill animals to provide organs for humans? Animals are already bred and killed for food, clothing and many other products, including a variety of medical materials. The use of porcine insulin or pig heart valves has been socially and morally acceptable for decades (19). Yet some people argue that animals have rights too and deserve equal consideration with human beings (20). They further argue that we should not raise animals for food or other products, or test new cosmetics on them. Animal rights activists also oppose the use of animals for medical experimentation (21). Nonetheless, most people seem to believe that a human being is quite distinct from and far more valuable than any animal. And the reality is that several billion animals are killed annually for food, so that the death of a few thousand animals yearly, so that their organs can be used to save people's lives, does not seem highly objectionable.

One can, of course, argue that xenotransplantation in humans is not ethically justifiable given the limitations of our current knowledge. Hastillo et al. (22) conclude that, because of these limitations, "this is a route not yet to trod." However, progress in medical research has already provided insights into how immunological barriers to xenotransplantation might be overcome. In time, such research may well provide the knowledge needed for successful clinical trials.

Guidelines for the conduct of animal research and its oversight by institutional committees and regulatory agencies are already in place in most of the Western world. These include assurances that the research proposal is sound, that the need for animal subjects is minimized, and that the animals are maintained in humane conditions and killed without pain.

Informed consent must, of course, be obtained from the human patient being offered xenotransplantation, who must be told of its experimental nature and its chances for success and potential side effects. Some patients might reject the whole idea of cross-species transplantation as inhumane and degrading (23). These and other issues raised by the basic and clinical research aspects of xenotransplantation are discussed by Caplan (24), who concludes as follows:

> The scarcity of organs and tissues from human sources is real, growing, and unlikely to be solved by any other alternative policies or approaches in the foreseeable future. If xenografting must be explored as an option, then the moral justification for doing basic and clinical research involving animals is that it would not be possible to learn about the feasibility of overcoming immunologic and physiologic problems without using animals, and that animals are to be used instead of human subjects whenever possible, since human beings have more moral worth than do animals. If xenografting evolves into a therapy, then provisions must be made for ensuring the welfare and health of the animals that would be bred, raised, and killed to supply organs and tissues to human beings.

Judaism's Prohibition of Cruelty to Animals

The Jewish attitude toward animals has always been governed by the consideration that they too are God's creatures and that *His tender mercies are over all His works* (Psalms 145:9). Not only is cruelty to animals prohibited, but humaneness, compassion and mercy to animals are demanded of man by God. God *gives to the beast its food* (Psalms 147:9) . . . *causes the grass to spring up for the cattle* (ibid. 104:14) . . . *satisfies every living thing* (ibid. 145:16), and *preserves man and beast* (ibid. 36:7). God's concern extends from the lion, king of the beasts, to the raven, one of the most despised of birds (Job 38: 39–41). When Moses obtained water from the rock by divine intervention, the water was to give drink to *the congregation and their cattle* (Numbers 20:8). One reason for the commandment to let the fields lie fallow in the Sabbatical year is that the food which grows naturally there during that year shall be *for thy cattle and for the beasts that are in thy land* . . . (Leviticus 25:7).

Animals must have their Sabbath rest the same as man (Exodus 20:10). In the repetition of the Decalogue in Deuteronomy, this teaching is reiterated (Deuteronomy 5:14), so that one of Britain's former chief rabbis (25) asserted that care and kindness to animals are of such profound importance for the humanizing of man that this duty has its place in the Decalogue. Thoughtfulness for animals as a religious duty is demonstrated in numerous biblical narratives. Rebekah proved that she was the proper wife for Isaac, son of Abraham the Patriarch, by the fact that she brought water not only for Abraham's servant Eliezer, but also for his camels (Genesis 24:14). The parable with which the prophet Nathan rebuked King David took for granted that a lamb can be a household pet to be treated kindly (2 Samuel 12:3). A righteous man is merciful and pays attention to the needs of his beast (Proverbs 12:10).

Numerous biblical commandments have as one possible explanation or allusion the prohibition of cruelty to animals. These include the prohibitions against muzzling an ox as it threshes, to deprive it of food while it is working (Deuteronomy 25:4), the slaughtering of an animal and its young on the same day (Leviticus 22:28), the eating of a limb cut off from a living animal (Genesis 9:4, Deuteronomy 12:23), as well as the command to release the mother bird from the nest before taking its young (Deuteronomy 22:6–7). The prohibition against muzzling the ox when he treads grain applies to all animals employed in labor. In his biblical commentary on Deuteronomy 22:10, Rabbi Abraham Ibn Ezra suggests that the reason for not plowing with an ox and a donkey together is that the ox, being the stronger, would pull harder and thus cause pain to the donkey. Moses Maimonides explains some of these laws as follows (26):

> It is likewise forbidden to slaughter [an animal] and its young on the same day (Leviticus 22:28), this being a precautionary measure in order to avoid slaughtering the young animal in front of its mother. For in these cases animals feel very great pain, there being no difference regarding this pain between man and the other animals. For the love and the tenderness of a mother for her child is not consequent upon reason, but upon the activity of the imaginative faculty, which is found in most animals just as it is found in man. This law applies in particular to ox and lamb, because these are the domestic animals that we are allowed to eat and that in most cases it is usual to eat . . . .

Ancient biblical commentary suggests that Moses and David were chosen as leaders because God noted their gentle and understanding treatment of their flocks. For example, it is told how Moses, while still his father-in-law Jethro's shepherd, sought out a stray lamb and tenderly carried the tired creature in his arms back to the fold. A voice from Heaven cried out: "Thou art worthy to be My people's pastor" (Exodus Rabbah 2:2). When Balaam struck his donkey, an angel rebuked him, saying: *Wherefore hast thou smitten thine ass these three times?* (Numbers 22:32) This verse is a classical text for the preaching of humane treatment of animals. Castration or emasculation of animals is also prohibited (Leviticus 22:34).

The major biblical source for the prohibition of cruelty to animals is the law that if one sees an animal staggering under a burden too heavy for it, one must stop and help unload it, even if the animal belongs to one's enemy (Exodus 23:5). This law shows a humanitarian motive toward the animal and a charitable motive toward the enemy. The law is codified by Maimonides, who rules that a person is enjoined to unload the burden from an animal that is crouching under the weight of the burden even if the owner is not present with the animal and even if the animal belongs to a heathen (27). Maimonides explains the prohibition of cruelty to animals as follows:

> As for the dictum of the sages: [To avoid causing] suffering to animals is [an injunction to be found] in the Torah — in which they refer to its dictum, *wherefore hast thou smitten thine ass*? (Numbers 22:32) — it is set down with a view to perfecting us so that we should not acquire moral habits of cruelty and should not inflict pain gratuitously without any utility, but that we should intend to be kind and merciful even with a chance animal . . . except in case of need — *Because thy soul desireth to eat flesh* (Deuteronomy 12:20), for we must not kill out of cruelty or for sport . . . (28).

Maimonides here clearly prohibits hunting for sport, accepting it only to satisfy hunger. In ancient times, however, some Jewish sects were strictly vegetarian. In fact, meat consumption is not sanctioned in Genesis until after the Flood. Man and animals were originally vegetarians according to the Talmud (Tractate Sanhedrin 59b), although the sacrificing of animals to God had been previously allowed (Genesis 1:29, 9:3). After Noah and his family saved the animals from extinction, God made a concession to man by giving him the right to consume meat (Genesis 9:3), provided the animals are humanely slaughtered. The Jewish method of ritual slaughter, particularly the laws that the knife be exceedingly sharp and without the slightest notch, is motivated by consideration for the animal, because this method is the most painless.

The Talmud, both in its legal (halachic) and homiletical (aggadic) portions, refers frequently to the mandate to be kind to animals and the prohibition of cruelty to animals. The Talmud states that wagonettes were made for rams so that their tails would not knock against rocks (Shabbat 54b). Furthermore, straps were placed on the legs of fowl to prevent the legs from knocking each other. A jaw bar was placed around the neck of a donkey with a bruise to prevent it from chafing it afresh and to allow it to heal (ibid.). After a ewe was sheared, a compress saturated in oil was placed on its forehead so that it should not catch cold. When a ewe kneeled for lambing, two oily compresses were made for her: one was placed on her forehead and the other on her womb so that she should be warmed. (ibid).

The Talmud also asserts that one helps fledglings ascend into or descend from a hen coop by overturning a basket for them in front of the coop (Shabbat 128b). One may assist an animal in giving birth on the Sabbath, and the newborn calf or lamb or other baby animal is held so that it will not fall on the ground. One also blows into the baby animal's nostrils to clear them of mucus and puts the teat into its mouth so that it can suck (ibid.).

One may desecrate the Sabbath and Jewish holidays to relieve the suffering of an animal, since the prohibition of cruelty to animals is biblical and takes precedence over rabbinically enacted Sabbath laws. To save animals from suffering is regarded as a stronger reason for desecrating the Sabbath than to save oneself from personal loss (Shabbat 117b). A person should not buy an animal or a bird unless he can properly provide for it (Jerusalem Talmud, Ketubot 4:8). A man is forbidden to eat before he gives food to his beast (Berachot 40a and Gittin 62a). A man who confined his neighbor's animal in a place exposed to the sun so that it died of sunstroke was held liable (Sanhedrin 76a).

The story is told of a calf, taken to be slaughtered, that broke away and hid its head under the skirts of Rabbi Judah the Prince. He said to it: "Go, for this wast thou created." Thereupon they said in Heaven: "Since he has no pity, let us bring suffering upon him." So Rabbi Judah suffered from a toothache for thirteen years; he was cured when he saved the lives of a litter of kittens (Baba Metzia 85a).

Animal Experimentation in Jewish Law

Despite the central importance placed on kindness to animals in Jewish tradition, the forward-looking Rabbi Moses Isserles (1510 – 1572), known as Rama, ruled that any activity necessary for medical or other useful purposes is excluded from the prohibition of cruelty to animals (29). He made this ruling in the context of another central tradition in Jewish thought: that the world and everything in it was created by God to serve humanity and human needs. Jakobovits (30) noted that none of the 15th century sources upon which Isserles based his ruling actually specify any medical use to which living animals can be put. Nevertheless, all subsequent permissive rabbinic rulings on animal experimentation for medical research are based on this statement by Isserles that, for medical or other useful purposes, the prohibition of cruelty to animals does not apply.

In the 18th century, Rabbi Jacob Reischer (1670 – 1733) was asked whether or not a Jewish physician is permitted to test the effects of a new drug on an animal, such as a dog or cat, in order to discover whether it might prove injurious or even fatal before applying it to human beings. His answer was strongly affirmative and was based on several earlier responsa (as was that of Isserles) that anything required for a useful purpose for mankind, including medical uses, is excluded from the biblical prohibitions of wanton destruction (based on Deuteronomy 20:19) and cruelty to animals (31). Reischer asserted that if the Sabbath must be desecrated to save a human life, the prohibition of cruelty to animals must also be set aside for the same reason.

In the 19th century, Rabbi Jacob Ettlinger (1798 – 1871) expressed the view, in accord with the permissive ruling of Isserles, that the prohibition of cruelty to animals is waived for any medical or useful purpose is limited to medical needs and is not valid for financial gain (32).

In the 20th century, rabbinic opinions have generally permitted animal experimentation for medical research, and the use of animals to save human lives. These opinions are cited and discussed in detail by Bleich (33), Friedman (34), Chaphutta (35), Steinberg (36), Metzger (37) and Cohen (38). These new rulings maintain the Jewish religious tradition that forbids any act which causes pain or discomfort to an animal unless that act satisfies a legitimate human need. Specifically, animal pain is "sanctioned only for medical purposes, including direct therapeutic benefit, medical experimentation of potential therapeutic value and the training of medical personnel" (33). Clearly, the use of animal organs, including those from pigs, to save human lives would be included in this list. One rabbinic responsum permits the raising of pigs for medical research (39). Otherwise there are no specific responsa on this issue yet. However, the principles of Jewish medical ethics discussed here make it highly probable that such responsa, if and when they are published, will rule permissively, in view of the life-saving nature of xenotransplants.

Summary and Conclusion

Judaism espouses the concept that everything that was created in this world by God was created to serve mankind. Thus, for example, certain animals, in accord with Jewish dietary laws, may be used for food, provided that they are humanely treated and slaughtered. Pigs are a noted exception with respect to their use as food by observant Jews. But the use of any animal as a source of hormones (e.g., insulin and growth hormone) or tissues for implantation (e.g., heart valves), or organs for transplantation to save human lives would be sanctioned in Judaism. Ethical scientific experiments upon laboratory animals, in medical research that might lead to a cure for a disease, are also sanctioned in Jewish law as a legitimate utilization of all animals for the benefit of mankind. However, animal experimentation and related usage of animals is permissible in Jewish law only if its purpose is to obtain practical benefits for mankind and not simply the satisfaction of intellectual curiosity. And every effort must be made to eliminate or minimize the pain that might be experienced by these animals.

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Hickman-Broviac Catheter-Related Infections in Children with Malignancies

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Abstract

Infectious complications are frequently encountered following Hickman-Broviac (H-B) catheter insertion. The medical records of 164 children with malignancies who underwent H-B catheter insertion from March 1, 1988 to December 31, 1997 were reviewed retrospectively. During a 35,697 catheter-day period, 77 catheter-related infections occurred, including 50 catheter-insertion-site infections and 27 bloodstream infections. The risk for the development of catheter-related infections was 2.15 per 1000 catheter-days (1.4 and 0.75 per 1000 catheter-days for catheter-insertion-site and bloodstream infections, respectively). In 17 (63%) of 27 episodes of bloodstream infections, antimicrobial treatment controlled the infection without catheter removal. A previous catheter-insertion-site infection caused by *Staphylococcus epidermidis* ($p=0.01$), the occurrence of mechanical catheter complications ($p=0.007$), and a normal coagulation status of the host ($p=0.03$) were significantly associated with the development of catheter-related bloodstream infections. H-B catheters remain important in pediatric oncology. Due to the significant morbidity associated with the development of catheter-related bloodstream infections, risk factors found to increase the incidence rate of such infections must be identified and properly managed. **Key Words:** Hickman-Broviac catheters, bloodstream infections, children, malignancies.

Introduction

Central venous catheters are widely used in children with malignancies. First described by Broviac (1) in 1973 and later modified by Hickman (2) in 1979, Hickman-Broviac (H-B) catheters constitute a useful tool for administration of chemotherapy, antimicrobial agents, blood products, hydration and total parenteral nutrition (3). Advantages over the usage of peripheral venous catheters include reduction of development of chemotherapy-induced dermatitis and improvement of the patient's quality of life, due to the avoidance of recurrent venipunctures (3). However, H-B catheter usage may be complicated by the development of bloodstream and catheter-insertion-site infections, and mechanical complications. The development of such infections in children with malignancies is a significant risk, due mainly to their deficient immune mechanisms (3). Therefore, identification of risk factors associated with the development of catheter-related infections in these patients is imperative. We present our 10-year experience on the use of H-B catheters in children with malignancies. In addition, the associated risk factors for the development of catheter-related infections and possible mechanisms accounting for such complications are discussed.

Patients and Methods

Patients

All children 14 years old or younger with a malignancy, who underwent H-B catheter insertion for therapeutic and/or supportive purposes at the Department of Oncology of the Aglaia

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Kyriakou Children's Hospital from March 1, 1988 to December 31, 1997 were identified through a computerized database system. Patients who received more than one H-B catheter were excluded from the study. Patients were followed from the time of catheter insertion to the time of catheter removal (if any), or the most recent follow-up, whichever occurred first. The medical records of the patients were reviewed in detail and the following information was collected: age at the time of catheter insertion, sex, underlying disease, date of catheter insertion, vein of catheter insertion, usage of antimicrobial prophylaxis, date of catheter removal (if any), and reason for catheter removal. In cases where catheter-related infection developed, additional information was collected, including date of development of catheter-related infection, presence of fever, signs of inflammation at the catheter-insertion-site, neutropenia, coagulation status, microbiological reports, antimicrobial treatment, and outcome of the patient. The study was approved by the scientific committee of Aglaia Kyriakou Children's hospital.

Definitions

Fever was defined as a temperature of 38°C or more that was unrelated to the administration of blood products or other pyrogenic substances. Routine fever work-up included catheter-insertion-site cultures, blood cultures through the catheter, and peripheral blood cultures. Neutropenia was defined as an absolute neutrophil count of less than 500/µL. Abnormal coagulation status was defined as a prothrombin or partial prothrombin time of more than 3 times the values of healthy control blood donors and/or as an absolute platelet count of less than 50,000/µL. Bloodstream infection was defined as isolation of a pathogen from the blood at least once, except for coagulate-negative staphylococci for which at least two positive cultures in a 72-hour period were required. An infectious episode that developed within 30 days of an initial episode was counted as part of that episode. Definite catheter-related bloodstream infection was defined as presence of fever along with a positive blood culture obtained through the catheter in association with a negative blood culture obtained through a peripheral vein (3, 4). Probable catheter-related bloodstream infection was defined as fever along with a positive blood culture obtained through the catheter and a positive blood culture obtained peripherally with no other focus of infection (3, 4). Catheter-insertion-site infection was defined as signs of inflammation at the catheter-insertion-site (e.g., redness, edema, warmth, tenderness, discharge) and pathogen isolation from the catheter-insertion-site discharge with or without fever (3, 4). Mechanical catheter complications included catheter translocation, dislodgment, obstruction, and malfunction, as well as rupture of the catheter and hematoma at the site of catheter insertion.

Clinical Methods

The right atrial catheters used for venous access were Silastic subcutaneously tunneled H-B catheters (Bard Co., Salt Lake City, UT). All catheters were placed in the operating room by the same team of pediatric surgeons. Antimicrobial prophylaxis consisted of either cefotaxime 50 mg/kg or vancomycin 10 mg/kg, administered intravenously in a single dose within one hour prior to catheter insertion. In the postoperative period, the site of insertion was cleansed with povidone-iodine on a daily basis; following patient's discharge, cleansing was carried out every 72 hours. Following cleansing, povidone-iodine ointment and sterile dressing were applied locally. Catheter dressings (gauze or clear plastic dressings) were changed in hospitalized patients twice per week and in outpatients once per week. The catheter was flushed once daily with sterile heparinized saline (500 IU heparin in 3 mL of normal saline), and the injection cap was changed weekly. Routine surveillance cultures were not performed. Whenever patients had fever and/or neutropenia, catheter-insertion-site cultures, blood cultures through the catheter and peripheral blood cultures were attempted. Treatment of catheter-related infections consisted of a 10 – 14 day IV course of either vancomycin 10 mg/kg b.i.d. or ceftazidime 50 mg/kg t.i.d. administered through the catheter. Antimicrobial treatment was considered successful in cases of negative blood and catheter-insertion-site cultures, with no catheter removal required for infection control and treatment. A catheter was removed when fever persisted for 72 hours or more and/or positive blood cultures (either through the catheter or peripherally) were obtained beyond 72 hours of antimicrobial treatment based on susceptibility pathogen testing. Mechanical complications were managed by repair of the catheter, if damaged, movement of catheter position, relief of occlusion or replacement of the device, as appropriate.

Statistical Analysis

An intention-to-treat statistical analysis was used in this study. All statistical analyses were two-tailed. Odds ratios were used as the measure of association, Z-scores were calculated (5), and corresponding p-values obtained. For bloodstream infections, the time to the event was used in a Kaplan-Meier survival analysis (6), the survival time being the infection-free interval. A univariate analysis searching for risk factors for bloodstream infections was conducted, including the following variables: age, sex, underlying disease, neutropenia, coagulation status, catheter-insertion-site infections, specific pathogens involved in catheter-insertion-site infections, and mechanical catheter complications. Multivariate analysis used stepwise forward logistic regression analysis with days of follow-up as a covariate, predictor factors as independent variables, with the probability of first infection as the dependent variable (7). In the multivariate logistic regression analysis, each patient was observed until the first episode of catheter-related infection. Categorical variables were studied using Fisher's exact test for proportions with appropriate degrees of freedom. In the analysis of quantitative variables, Student's unpaired t-test was used for variables with normal distributions and the Mann-Whitney U-test for variables with non-normal distributions. Values of $p \leq 0.5$ were considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS for Windows '95, version 7.5).

Results

During the study period, 185 children with H-B catheters were identified. Twenty-one patients were either excluded due to multiple H-B catheter insertions (18 patients) or lost to follow-up (3 patients). Therefore, the study population comprised 164 patients, of whom 84 were girls (51%) and 80 were boys (49%). Patients' median age was 5 years (range, 2 months to 14 years). Their characteristics are listed in Table 1. Inserted catheters included Broviac catheters in 133 (81%) patients and Hickman catheters in 31 (19%) patients. External and internal jugular veins were used in 130 (79%) patients and 34 (21%) patients, respectively. Catheters were inserted for a median of 235 days (range, 7–690 days). Overall, 35, 697 days of catheter usage were studied.

During the study period, 63 (38%) of the 164 children developed a total of 77 episodes of catheter-related infections, including 50 catheter-insertion-site infections and 27 bloodstream infections. The median number of catheter-related infections per patient infected was 1 (range, 1–2 catheter-related infections). In particular, 36 patients developed catheter-site infections only, 14 developed catheter-insertion-site infection followed by bloodstream infections, and 13 developed catheter bloodstream infections only. Twenty (40%) and 30 (60%) out of 50 catheter-insertion-site infections developed in the exit portion and tunnel, respectively. The number of probable episodes, and definite episodes, of catheter-related bloodstream infections were 17 (63%) and 10 (37%) episodes, respectively.

TABLE 1

Baseline Characteristics of Patients

	No. of patients (%) (n=164)
Age	
≤3 years	42 (26)
>3 years	122 (74)
Sex	
males	80 (49)
females	84 (51)
Underlying disease	
leukemia	107 (65)
solid tumors	57 (35)
Mechanical complications	
translocation	5 (3)
dislodgment	13 (8)
obstruction	7 (4)
malfunction	7 (4)
rupture	2 (1)
hematoma	8 (5)
Absolute neutrophil count	
$<100/mm^3$	15 (9)
$100-500/mm^3$	21 (13)
$>500/mm^3$	128 (78)
Coagulation status	
normal	135 (82)
abnormal	29 (18)

The risk for the development of catheter-related infections was 2.15 per 1000 catheter-days, and 1.4 and 0.75 per 1000 days for catheter-insertion-site and bloodstream infections, respectively. The median time interval from the time of catheter insertion to the onset of catheter-related infection was 30 days (range, 1–400 days). Catheter-insertion-site infections occurred at a median of 27.5 days (range, 1–400 days) following catheter insertion, while catheter-related bloodstream infections occurred at a median of 31 days (range, 5-390 days) following catheter insertion. Pathogens detected in catheter-related infections are summarized in Table 2. *Staphylococcus epidermidis* was the predominant isolate in patients with either catheter-insertion-site infections or catheter-related bloodstream infections, independent of age, catheter-insertion-vein, neutropenia, and coagulation status of the patient.

TABLE 2
Isolated Pathogens in Catheter-Related Infections

Pathogen	Catheter-insertion-site infections	Bloodstream infections
Staphylococcus epidermidis	30 (60)	15 (56)
Staphylococcus aureus	15 (30)	5 (18)
Escherichia coli	2 (4)	2 (7)
Pseudomonas aeruginosa	2 (4)	1 (4)
Klebsiella pneumoniae	0 (0)	2 (7)
Salmonella	0 (0)	1 (4)
Candida albicans	1 (2)	1 (4)

Values in parentheses represent %

Antimicrobial treatment consisted of vancomycin in 60 (78%) of 77 episodes of catheter-related infections and cefotaxime in the remaining 17 (22%) patients. Of the 77 episodes of catheter-related infections, 63 (82%) responded promptly to antimicrobial treatment while catheter removal was required in 14 of them (18%). In particular, treatment was successful in 46 (92%) of the 50 episodes of catheter-insertion-site infections, while catheter removal was required in 4 (8%). Pathogens responsible for the catheter-insertion-site infections requiring catheter removal included *S. epidermidis* (n=2) and *Staphylococcus aureus* (n=2). Only two of the four patients needed catheter replacement and no recurrent infection was documented. Among the 27 episodes of bloodstream infections, treatment was successful in 17 (63%), as compared to 10 (37%) episodes, where removal was required. The following pathogens were detected in the catheters removed from patients with bloodstream infections: *S. epidermidis* (n=5, 50%), *S. aureus* (n=3, 30%), *Pseudomonas aeruginosa* (n=1, 10%), and *Candida albicans* (n=1, 10%). In total, catheters had to be removed in 9 (15%) out of 60 episodes treated with vancomycin and in 5 (29%) out of 17 episodes treated with cefotaxime (p=0.15).

Mechanical catheter complications occurred in 42 (26%) of the 164 patients. In 24 (57%) of the 42 patients with mechanical catheter complications, the catheter had to be removed, while flushing with heparin solution and repositioning of the catheter was required in 10 (24%) and 8 (19%) of them, respectively. In total, catheters were removed in 149 patients (91%) of the 164 patients, at a median of 235 days (range, 7–690 days) following catheter insertion. At the end of the study period, 15 catheters (9%) were still in place. Reasons for removing a catheter were: (1) the completion of chemotherapy in 96 out of 149 patients (64%); (2) mechanical complications in 24 out of 149 patients (16%); (3) death unrelated to catheter insertion in 19 out of 149 patients (13%); and (4) catheter-related infections in 10 out of 149 patients (7%). During the study period, no episode of death due to catheter-related infections occurred among the 164 patients studied. However, 2 out of 27 patients (7%) with bloodstream infection expired at 690 and 400 days following catheter insertion, of disseminated carcinomatosis and massive pulmonary embolism, respectively.

Risk Factors for Catheter-Related Bloodstream Infections

A univariate statistical analysis searching for risk factors for the development of catheter-related bloodstream infections in children with malignancies was conducted (Table 3). On logistic regression analysis, the following parameters emerged as statistically significant risk factors for the development of catheter-related bloodstream infections: a prior catheter-insertion-site infection with *S. epidermidis* (OR=3, 95% CI: 1.2–7.1, p=0.01), the occurrence of mechanical catheter complications (OR=4.1, 95% CI: 1.7–9.8, p=0.007) (Figure), and a normal coagulation status of the patient (OR=6.7, 95% CI: 1.6–51.8, p=0.03).

Discussion

H-B catheters are widely accepted as an effective means for vascular access over an

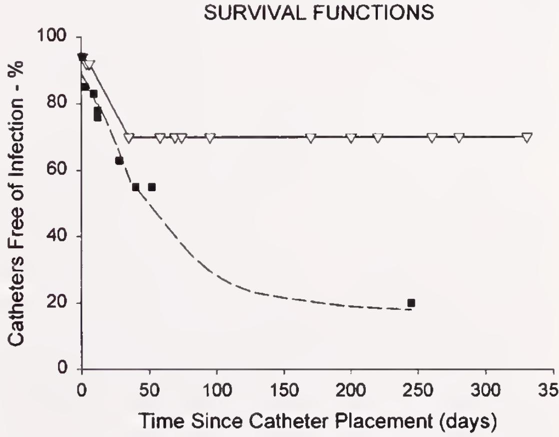

Figure. Kaplan-Meier survival curves of H-B catheters without mechanical catheter complications (open triangles and solid black line) and H-B catheters with mechanical complications (gray squares and dashed line). Survival curve indicates percentage of catheters that remain infection-free over time. A catheter is withdrawn from the analysis when infection first occurs in the catheter. Curves show statistically significant difference (p=0.03 by log-rank test).

TABLE 3

Univariate Analysis for Risk Factors for Catheter-Related Bloodstream Infections

	Bloodstream Infections N (%)	Catheter-days	Infection rate /1000 catheter-days	OR	CI	p
Age						
≤3 years	6 (22)	8327	0.7	1.2	0.4–3.3	0.8
>3 years	21 (78)	27370	0.7	1.00		
Sex						
females	12 (44)	19057	0.6	0.9	0.6–1.5	0.5
males	15 (56)	16640	0.9	1.00		
Mechanical complications						
yes	14 (52)	7561	1.8	4.1	1.7–9.8	0.001
no	13 (48)	28136	0.4	1.00		
Coagulation status						
normal	26 (96)	29559	0.9	6.7	1.6–51.8	0.02
abnormal	1 (4)	6138	0.2	1.00		
Catheter colonization						
yes	14 (52)	11099	1.3	2.9	1.2–6.9	0.01
no	13 (48)	24598	0.5	1.00		
Neutropenia						
yes	6 (22)	7936	0.7	0.9	0.4–2.1	0.5
no	21 (78)	27761	0.7	1.00		
Disease						
leukemia	19 (70)	22754	0.8	1.3	0.5–3.2	0.6
solid tumors	8 (30)	12943	0.6	1.00		

* Comparisons were performed with Fisher's exact test, OR=odds ratio; CI=95% confidence intervals.

extended time period in children with malignancies. However, their wide usage has been associated with the subsequent development of infectious and mechanical complications (8 – 12). Previous reports have documented an infectious complication rate of 0.1 –0.7 per 1000 catheter-days (12 – 20). The present study demonstrates that H-B catheters constitute a safe therapeutic intervention in children with malignancies. The rates of catheter-insertion-site infections (1.4 per 1000 catheter-days) and catheter-related bloodstream infections (0.75 per 1000 catheter-days) were low and comparable to those previously reported (2, 11, 14, 17).

Mechanical complications of H-B catheters have been well recognized as potentially associated with the development of bloodstream infections (20 – 22). The present study showed that mechanical complications are associated with a 4-fold increased risk for bloodstream infections as well as for catheter-insertion-site infections. The underlying cause for such an association might be inflammation following local trauma which predisposes bacterial colonization and growth at the site.

The development of a prior catheter-insertion-site infection was associated with a 3-fold increased risk for subsequently developing a bloodstream infection, especially when the colonizing organism was a coagulase-negative staphylococcus. Biofilm, the thrombin sleeve around the catheter, produced by the inflammatory reaction of the organism, is the main site of staphylococcal colonization (3). Coagulase-negative staphylococci adhere to fibronectin and not to fibrin of the biofilm (3, 23 – 29). The ability of this pathogen to colonize catheters is due to its prevalence on the skin and its capacity to adhere to and degrade catheter material, as well as to produce a self-protective glycocalyx substance or extracellular slime (3, 23 – 29). Microbial organisms such as slime-producing coagulase-negative staphylococci enhance their adherence by producing this glycocalyx material, which constitutes the microbial substance of the biofilm. Following the formation of the biofilm around the catheter, the embedded organisms are highly protected from antimicrobial agents, neutrophils and macrophages (23 – 25). Consequently, colonizing organisms can easily pass to the bloodstream and cause bacteremia. There is conflicting evidence regarding the value of antimicrobial prophylaxis administered prior to H-B catheter insertions (11, 30, 31). All patients in the present study had received prophylactic agents intravenously prior to catheter insertion.

In the present study, patients with normal coagulation status had a 7-fold higher risk for developing a bloodstream infection, as compared with patients with abnormal coagulation status. A possible explanation for this finding might be that the reduced formation of the fibrin and fibronectin layer of the biofilm in patients with abnormal coagulation status prevents bacterial adherence on the catheter material (27–29). Furthermore, catheter clotting was more probable in patients with normal coagulation status, predisposing them to catheter-related bloodstream infections.

Despite the previously reported increased bloodstream infection rate among patients younger than three years of age, the present study did not confirm these results (9). A possible explanation might be the small number of such patients in the present study. Moreover, in the present study, febrile patients with H-B catheters were found to be at significant risk for systemic bacterial infections, regardless of their absolute neutrophil count. However, Hiemenz et al. reported that the insertion of central venous catheters was associated with a 10-fold increased rate of bloodstream infection rate among patients with normal absolute neutrophil counts as compared to neutropenic patients (32). Indeed, the failure to reveal an association between neutropenia and bloodstream infections supports the view that H-B catheter insertion independently enhances the incidence of bacteremia.

In the present study, no significant association was documented between specific pathogens and the risk of treatment failure after bloodstream infections. In previous studies, catheter-related bloodstream infection with *S. aureus* was associated with a higher risk of treatment failures and therefore for subsequent need for catheter removal (8, 33).

Factors that were significantly associated, in the present study, with the development of catheter-related bloodstream infections included a prior catheter-insertion-site infection with *S. epidermidis*, the occurrence of mechanical catheter complications, and a normal coagulation status of the patient. It is suggested that in children with malignancies, who develop an H-B catheter-insertion-site infection, empiric antistaphylococcal treatment should be prescribed in association with avoidance of catheter manipulations. An interesting finding of the present study was that in the majority of cases with catheter-related bloodstream infections, catheter removal was not required in order to control infection. Antimicrobial treatment was highly effective and no child died of catheter-related infection.

Limitations of our study were the exclusion of patients with multiple H-B catheter insertions, which may bias toward a more favorable outcome of patients selected. Future prospective studies might be needed to investigate risk factors for catheter-related bloodstream infection in this subset of patients. Additionally, the retrospective methodology could not, with certainty, establish direct causal relationships.

In conclusion, H-B catheters remain a safe and effective tool in the management of pediatric malignancies. This finding implies the need to recognize and properly manage risk factors for bloodstream infections in children with malignancies, in whom H-B catheters have been inserted.

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Adenocarcinoma of the Urachus Masquerading as a Right Lower Quadrant Mass:

A Case Report

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Abstract

We report a patient who presented initially with a right lower quadrant mass which was attached to the anterior abdominal wall. The final pathological diagnosis was adenocarcinoma of the urachus, an exceedingly rare bladder tumor. **Key Words:** Urachal anomalies, urachal carcinoma, lower quadrant mass, adenocarcinoma.

Urachal carcinoma is an unusual cancer with an incidence of approximately 1% of all bladder cancers. Occurring in approximately 1 in 5 million adults, it represents approximately 0.01% of all cancers (1). It may occur at any age from the late teens to the eighth decade, with a predilection for males (2). While the typical presentation for this condition involves hematuria and irritative voiding symptoms, we present such a case which presented initially as a right lower quadrant mass with attachments to the anterior abdominal wall. It is this atypical presentation of an exceedingly rare tumor that challenges clinicians to consider adenocarcinoma of the urachus in the differential diagnosis of a right lower quadrant mass.

Case Report

The patient is a 57-year-old man who complained of a 3-month history of white discharge in the urine without sediment. He also claimed decreased force of stream and occasional double voiding, as well as intermittent perineal pain. He denied prior medical history. He had had a cholecystectomy in 1980.

On physical examination, the patient was afebrile, with a blood pressure of 130/70 mm Hg and a pulse of 86/minute. Cardiac and pulmonary examinations were unremarkable. Abdominal examination revealed normally active bowel sounds without evidence of guarding or rebound tenderness. Palpation in the right lower quadrant revealed a palpable soft mass between the anterior superior iliac spine and the umbilicus. Auscultation over the mass revealed no evidence of bowel sounds. The testicles were descended bilaterally and the phallus was circumcised. On digital rectal examination, the prostate was without masses and was estimated to be approximately 25 grams. The stool was hemoccult negative.

Prior symptoms of urinary frequency and straining to void were evaluated by uroflowmetry. His uroflow was 8 cc/sec (normal range: greater than 15 cc/sec). Urinalysis revealed 5 rbc/hpf. Urine cytology was negative. Flexible cystoscopy revealed normal bladder mucosa and the suggestion of an inflammatory lesion in the bladder apex possibly consistent with an extrinsic mass or a colonic fistula. This inflammatory lesion could not be biopsied cystoscopically. The differential diagnoses considered at this point are listed in Table 1. CT scan of the abdomen and pelvis revealed a right lower quadrant mass

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TABLE 1

Differential Diagnosis of Right Lower Quadrant Mass

Adenocarcinoma of cecum
Adenocarcinoma of right colon
Cholecystitis
Colovesical fistula
Inflammatory bowel disease
Intussusception of the cecum
Mesenteric adenitis
Pancreatitis
Urachal remnant

thought to be of gastrointestinal origin abutting the bladder. The location of the mass on CT scan allowed for simple needle biopsy to be undertaken. CT-guided needle biopsy of the mass revealed fibrosis and microcalcification with no tumor cells seen.

The patient's complaint of persistent right lower quadrant discomfort over the ensuing weeks prompted laparoscopic exploration of the pelvic lesion. Operative findings noted a 1.0 cm by 1.0 cm mobile lesion at the right anterior bladder wall-peritoneal surface without attachments to the bowel or abdominal wall. Frozen section was consistent with colonic adenocarcinoma. The procedure was converted from laparoscopy to an open retroperitoneal surgical approach. Partial cystectomy was performed through a Pfannensteil incision approximately 2 cm above the pubis. Pathology revealed moderately differentiated colloid-type urachal adenocarcinoma which extended from the perivesical fat to the mucosa within the urachal remnant. The lesion was intramural, with the bladder mucosa being ulcerated and showing no primary changes (Figure). The final pathological diagnosis was adenocarcinoma of the urachal remnant and not a bladder wall adenocarcinoma. A postoperative CT scan at 3 months failed to reveal any mass lesions. Cystoscopic follow-up revealed no evidence of tumor.

Discussion

Urachal carcinoma accounts for less than 1% of bladder cancers and approximately 40% of vesical adenocarcinomas. More common in men, typical signs and symptoms include abdominal pain and mass, umbilical discharge, dysuria and/or hematuria (1 – 3). This patient had a diminished uroflow as part of his preoperative workup. Since urachal lesions typically involve the dome of the bladder and spare the bladder neck, it is unlikely that this patient's diminished uroflow is related to the urachal carcinoma. Cystourethroscopy revealed mild prostatic enlargement, which is the likely reason for the observed decreased uroflow.

Figure. Gross specimen demonstrating a glistening mucoid tumor mass involving the bladder wall and adjacent soft tissues.

To evaluate the significance of the findings on CT scan, colonoscopy was performed. Colorectal polyps were not observed, but some small internal hemorrhoids were noted. The patient's continuing abdominal pain and right lower quadrant mass led to the diagnostic laparoscopy, which revealed an extracolonic mass at the anterior bladder wall. The frozen section biopsy was consistent with colonic adenocarcinoma. Taken together, the most likely diagnosis was urachal adenocarcinoma, particularly since the underlying bladder mucosa was normal. The surgical procedure was converted from laparoscopy to an open retroperitoneal surgical approach, in order to perform a partial cystectomy.

The evaluation for a suspected urachal tumor should be similar to evaluation for any bladder tumor. Urinalysis, urine culture and cytology should be performed (3, 4), and a careful history and physical examination should be completed. The most common symptom is hematuria due to erosion of the tumor into the dome of the bladder.

Mucus, although common in the pathologic specimen, is only found in the urine in 15–33% of cases (4). Mucus or bloody discharge from the umbilicus has also been reported (3, 4). In general, lesions are often silent until they have reached an advanced stage.

Diagnostic cystoscopy is an important examination. Chest x-ray, computed tomograph (CT) of the abdomen and transurethral biopsy (if possible) are necessary prior to surgical resection. CT scan provides the most accurate diagnosis and staging for urachal carcinoma. This modality can demonstrate intra- and extravesical involvement, as well as surrounding pelvic lymph nodes (5). Approximately 60% of urachal tumors have regions of low attenuation, which suggests the high mucin content of these lesions. Nearly 50% of scans demonstrate curvilinear, punctate or scattered peripheral calcifications (4, 5). The CT scan can differentiate other lesions that may mimic urachal carcinoma (Table 2).

Cystoscopic appearance can be as follows: a polypoid or papillary mass on the bladder dome, or a bulge with normal overlying urothelium. The urachal opening may reveal bloody or gelatinous discharge (1, 2, 6). Histologic patterns of these tumors include glandular, colloid, papillary or signet ring configuration. Approximately 69% of urachal tumors are mucin-positive adenocarcinomas, 15% mucin-negative adenocarcinoma, 8% sarcoma, 3% squamous cell carcinoma and 2% others. Tumors can spread by direct extension to the space of Retzius, abdominal wall, peritoneum and bladder. Staging of this lesion has been proposed by Sheldon et al. and by others (Table 3) (1, 3). Muscle invasion is nearly always present. Local recurrence is noted in up to 80% of cases, while distant metastasis occurs late (3, 4).

Potential sites of urachal metastases include lungs, liver, bone and regional lymph nodes. CT scan may evaluate the liver and nodes. Chest x-ray, alkaline phosphatase, and/or bone scan should also be performed (2, 3).

The preferred treatment is wide local excision with partial or radical cystectomy. This approach should also include en bloc resection of the umbilicus and bilateral pelvic lymphadenectomy (3). To prevent local recurrence, it is very important to maintain wide margins during the resection. Sheldon et al. (1) noted that 21% of recurrences are in the pelvis while 16% occur in the bladder. Local recurrence typically occurs within the two years following initial surgery. Others have suggested radical cystectomy with pelvic node dissection as a preferred treatment. However, there is no significant survival advantage over partial cystectomy alone. Herr (7) suggests that survival is related to the stage of disease at presentation rather than the extent of surgical procedure. The overall five-year survival rate for urachal carcinoma is approximately 50%. Preoperative radiotherapy has also been examined with unproven usefulness. These tumors are relatively resistant to radiation therapy and chemotherapy (8, 9).

TABLE 2

Lesions That May Mimic Urachal Carcinoma

Adenocarcinoma of the cecum
Adenocarcinoma of the colon
Dermoid myoma
Ovarian carcinoma
Uterine myoma

TABLE 3

Staging of Urachal Carcinoma

Stage I — No invasion beyond the urachal mucosa
Stage II — Invasion confined to the urachus
Stage IIIA — Local extension into the bladder
Stage IIIB — Local extension into the abdominal wall
Stage IIIC — Local extension into the peritoneum
Stage IIID — Local extension into viscera other than the bladder
Stage IVA — Metastases to regional lymph nodes
Stage IVB — Metastases to distant sites

From Sheldon C, Clayman RV, Gonzalez R, et al. (1).

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Added in page proof: One year later, a local recurrence was removed. Radiotherapy and chemotherapy were administered.

Transient Headache and Impaired Vision after Intravenous Thyrotropin-Releasing Hormone in a Patient with Pituitary Macroadenoma

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Abstract

We report a case of transient headache and impaired vision following administration of intravenous thyrotropin-releasing hormone (TRH) to a woman with a non-functioning pituitary macroadenoma, visual field defect, and elevated thyroid-stimulating hormone (TSH). The symptoms lasted for two hours and then resolved without known sequelae. There are a few other reported cases of similar adverse reactions to neuroendocrine manipulation in patients with pituitary macroadenomas. This is the second reported case of such adverse reactions to TRH alone and the first in which the patient had prior elevation of TSH. **Key Words:** Thyrotropin-releasing hormone, pituitary macroadenoma, headache, primary hypothyroidism, impaired vision.

Introduction

PITUITARY FUNCTION TESTS are often performed in the evaluation of a macroadenoma, usually to assess pituitary reserve. Stimulation testing with synthetic releasing factors is generally well tolerated, except for the mild side effects associated with each agent (1–4).

There have been a number of reports of pituitary apoplexy, frontal headaches and amaurosis following administration of gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH), or insulin-tolerance test (ITT) alone or in combination (5–9). We report the onset of severe headache and impaired vision 5 minutes after pituitary testing with TRH, in a patient with a non-functioning pituitary macroadenoma and coexistent primary hypothyroidism.

Case Report

A 67-year-old woman presented to her ophthalmologist for visual difficulties. Formal visual field testing revealed a right temporal hemianopia and left lower temporal quadrantanopia. An MRI disclosed a 4.1 x 2.3 cm pituitary macroadenoma with suprasellar extension (Figure). She was referred to a neurosurgeon for a transsphenoidal resection of the tumor. Endocrine evaluation was requested prior to her surgery.

Her medical history was noncontributory. There was no history of hypertension or any known thyroid disease. She denied seizures, diplopia, or anosmia. Prior to an uneventful menopause at age 45, the patient had normal menstrual cycles. Family history for endocrine or autoimmune diseases was negative.

On physical examination, her blood pressure was recorded at 138/78 mm Hg, with a regular

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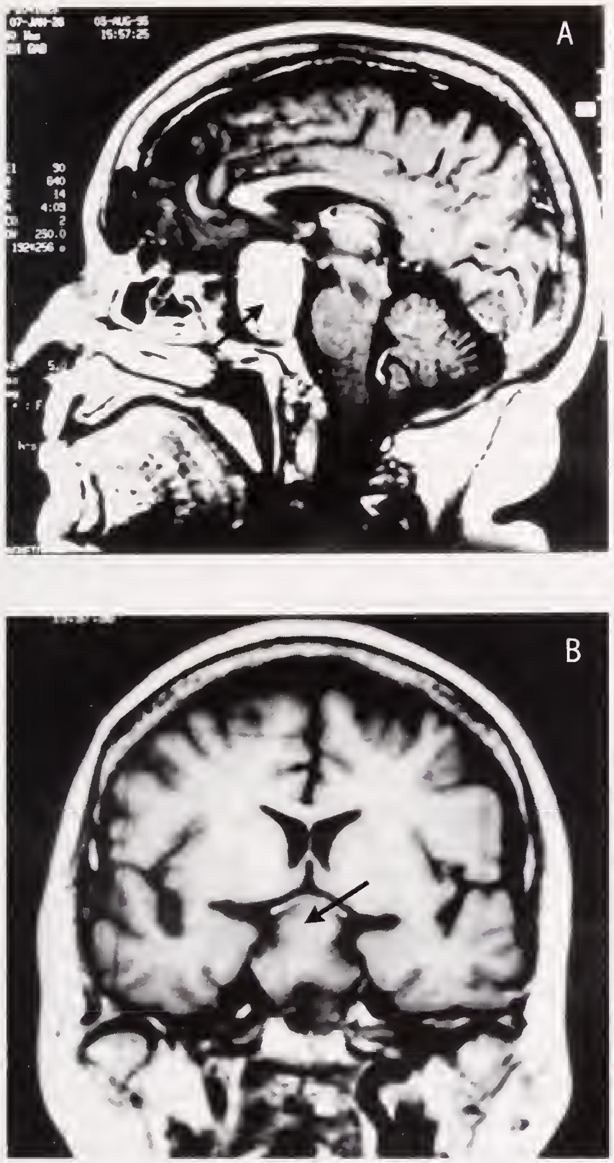

Figure. A magnetic resonance imaging of pituitary fossa showing 4.1 x 2.3 cm pituitary macroadenoma with suprasellar extension (arrow).

pulse of 72 beats per minute. There was no proptosis, and her extraocular movements were normal. The optic discs were flat. The right temporal visual field was cut. The thyroid was normal in size and without nodularity.

The rest of her examination was unremarkable. However, her pituitary function tests included the following results: TSH 33 IU/L (normal range 0.3 – 5.0), T_4 47.73 nmol/L (normal range 58.05 – 161.25), free T_4 11.09 pmol/L (normal range 18.06 – 38.7), prolactin 1.91 nmol/L (normal <0.91), follicular stimulating hormone 9 IU/L (normal range postmenopausal 34.3 – 95.8), luteinizing hormone 11 IU/L (normal range postmenopausal >20), AM cortisol 0.22 pmol/L (normal range 0.14–0.63), estradiol 73.4 pmol/L (normal range postmenopausal <216.53).

Our differential diagnosis considered the following possibilities: (1) a large pituitary adenoma associated with elevated TSH and low circulating thyroid hormone levels characteristic of primary hypothyroidism with marked thyrotroph hyperplasia; (2) chromophobe adenoma with secondary hypothyroidism with elevated levels of bio-inactive TSH (10); (3) coexisting chromophobe adenoma and primary hypothyroidism. The diagnosis of a TSH secreting tumor was not considered because of the low circulating thyroid hormone levels. Antithyroid antibodies were ordered. A TRH stimulation test was performed in an attempt to assess its usefulness in differentiating between the above possibilities.

Five minutes after the intravenous injection of TRH (200 µg TRH, Relefact Ferring Lab, Suffern, NY), the patient developed severe bifrontal headaches and blurring of vision. Her blood pressure remained unchanged. Visual acuity improved after 30 minutes and the blurring disappeared after 2 hours. One hour after TRH injection, examination of her visual fields was unchanged from baseline. However, since she continued to complain of headaches, a repeat MRI of sella turcica was ordered but, unfortunately, could not be obtained because of a mechanical problem with the machine.

Due to the persistent headache and concern about hemorrhage into the tumor, transsphenoidal surgery was performed eight hours after the TRH test. Pathology revealed a chromophobe adenoma without evidence of hemorrhage or infarction. Immunohistochemical staining of the tumor was negative for TSH, prolactin, and ACTH. On the third postoperative day, results of antithyroid antibodies were reported to be greater than 1200 IU/mL (normal <1.0). The alpha subunit was 1.6 mg/L (<1.2). The serum TSH levels after the TRH test were: 40.2, 71.8, 93.7, 95.8, 114.1, 93.9 (IU/L) at time 0', 15, 30, 60, 90, 120 minutes respectively.

The patient's visual fields recovered to nearly normal one week following surgery. She refused to consider a repeat TRH stimulation test.

Discussion

Side effects from intravenous TRH are usually mild. These have mainly included dryness of the mouth, flushing, a sensation of urinary urgency, abdominal and chest discomfort (2, 11) and transient elevation of blood pressure (1, 12). There are only a few case reports of transient amaurosis and headache after injection of TRH (5, 6, 8, 9). Except for one patient, all reported cases received other releasing factors and/or insulin, in addition to TRH. In our patient, the only administered releasing factor was TRH.

The results of TRH suggested primary hypothyroidism (high baseline TSH with brisk rise). The fact that the TSH levels remained elevated at two hours suggested a possible central component. Although most patients with pituitary lesions and hypothyroidism fail to respond to TRH, some may have a normal, delayed, or even exaggerated response in their levels of serum thyrotropin (13).

Autoimmune thyroid disease was confirmed during the immediate postoperative period when the preoperative laboratory test revealed the presence of markedly elevated antimicrosomal antibodies. Histological examination of the tumor did not reveal any TSH staining. Pituitary function testing revealed secondary hypogonadism.

A pituitary macroadenoma in a patient with an elevated TSH and positive thyroid autoantibodies can be seen in unusual cases of primary hypothyroidism with marked thyrotroph hyperplasia. This can masquerade as a prolactinoma because of the occasional associated hyperprolactinemia (14–20). Pituitary enlargement with suprasellar extension up to 8 mm has been reported with TSH levels of 50–100 IU/mL (15, 17). Interestingly, a brain scan revealed a 2x2 cm area of increased uptake of ^{99m}technetium in the area of sella turcica in a patient reported by Vagenakis et al. (18). Treatment consisted of exogenous thyroid hormone with radiologic documentation of shrinkage of the pituitary mass. Indeed, if surgery had not been deemed urgently necessary, a trial of thyroid hormone therapy would have been started to see if the pituitary mass decreased in size as TSH returned to normal.

It is of interest that all reported cases of adverse effect to TRH, or combined pituitary testing, were in patients with non-functioning pituitary macroadenomas. The one exception (9) was a growth-hormone-secreting microadenoma.

The fact that the acute onset of headache and impaired vision occurred 5 minutes after injection of TRH suggests that these symptoms were precipitated by the TRH itself. Such reactions to TRH are infrequent, occurring in 1:1000 patients tested (9). Possible explanations are: (1) vasospasm induced by TRH (TRH elevates levels of serum norepinephrine [11]) or (2) acute swelling of the pituitary following TRH, causing stretching of the dura and further pressure on the optic chiasm. The role of prior elevation of TSH in producing these unusual reactions to exogenous TRH is uncertain.

In retrospect, the TRH test did not add any important information in the differential diagnosis of our case. Due to the potential risk of TRH stimulation testing in patients with pituitary macroadenoma, it should be performed only if the benefit clearly outweighs the risk.

Conclusion

Intravenous TRH stimulation testing in a patient with a pituitary macroadenoma can, on rare occasions, result in serious side effects, including amaurosis and even pituitary apoplexy. This risk must be considered prior to such neuroendocrine testing in patients who might have pituitary macroadenomas.

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Student Corner

Souvenir from the Hamptons — A Case of Cutaneous Larva Migrans of Six Months' Duration

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Abstract

Cutaneous larva migrans is a distinctive serpiginous eruption caused by a reaction to burrowing hookworms. The infection is usually self-limited, normally lasting 2–8 weeks, but may persist for more than a year if misdiagnosed. Biopsies of the creeping eruption rarely reveal an organism. Thus, it is important for the infection to be recognized clinically, so that effective treatment may begin. We found topical thiabendazole to be fast and effective in treating this case of cutaneous larva migrans of six months' duration. **Key Words:** Cutaneous larva migrans, creeping eruption, ground itch, uncinarial dermatitis.

Case Report

A 35-YEAR-OLD MALE presented to the faculty practice complaining of an intensely pruritic rash of six months' duration on his neck. The patient first experienced these symptoms during the summer, shortly after sunbathing in South Hampton, New York, without a beach towel. Initial treatment with a topical steroid ointment offered no relief. Examination revealed an extensive, erythematous track measuring 2–3 mm in width on the posterior neck (Fig. 1). A more obviously undulating and serpiginous component to the track was present along the inferolateral aspect of the right side of the neck (Fig. 2). Erythematous papules studded the posterior neck and right retroauricular area. The remainder of the cutaneous examination was unremarkable. A biopsy specimen taken from the leading edge of the tract revealed a nonspecific dermatitis. Treatment with topical thiabendazole offered dramatic relief of the pruritus within 24 hours. On follow-up examination 2 weeks later, the eruption was significantly improved.

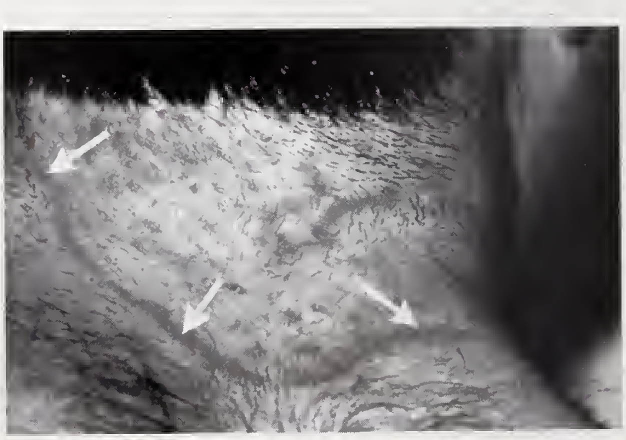

Fig. 1. Posterior neck. White arrows indicate an extensive, erythematous track.

Discussion

Cutaneous larva migrans, or creeping eruption, is a distinctive serpiginous cutaneous eruption caused by burrowing hookworms for which humans are the abnormal final hosts. If the clinical suspicion is low, the condition is often misdi-

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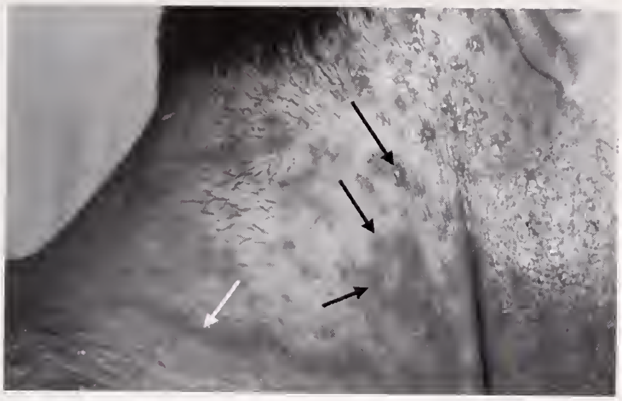

Fig. 2. Right side of the neck. White arrow indicates a serpiginous track continued from the posterior neck (see Fig. 1) and black arrows indicate erythematous papules studding neck.

agnosed. Although larva migrans is often thought of as a tropical infection, an increasing number of cases in cooler northern climates have been reported (1). The hookworms are endemic in tropical areas, but they have a worldwide distribution (2, 3).

In the United States, cutaneous larva migrans is most often caused by the larvae of the nematodes *Ancylostoma braziliense* and *Ancylostoma caninum*, hookworms of wild and domestic dogs and cats (4, 5). These worms are endemic in the central and southeastern United States, in Central and South America, and in other tropical climates. Because the larvae are located 1–2 cm ahead of the advancing edge of the lesion (1), biopsies rarely reveal an organism. In one study (6), larvae were found in only 8 out of 300 biopsy specimens. Thus, the clinical signs of this parasitic eruption are crucial for its correct diagnosis.

Typically, humans become infected when they have prolonged contact with warm, sandy, shady areas frequented by dogs and cats. Such contact, or the clinging of moist soil to the skin, allows the larvae time to penetrate through hair follicles or breaks in the skin. However, the larvae may penetrate unbroken skin by utilizing proteolytic enzymes (5, 7). Migration of the larvae is marked by tortuous, intensely pruritic, thin, elevated, erythematous tracts, 2–3 mm wide, containing serous fluid. Old tracts become dry and crusted (4, 8). Although migration generally begins after a short incubation period, the larvae may remain stationary for weeks or months (1). The larvae burrow several millimeters to a few centimeters each day, usually limited to a small area, and they may create wild patterns if many larvae are actively migrating. Migration occurs freely in the epidermis. However, the larvae rarely penetrate the basal layer into the upper dermis. It is postulated that the larvae do not possess the specific collagenases necessary to tunnel through the human epidermal basement membrane (5, 7).

The disease is usually self-limited. Most larvae die, if untreated, within 2–8 weeks, although larvae may rarely persist for up to 1 year. Leeming (9) theorizes that the difference in survival times may be due to the climate the larvae experience. Warmer climates may stimulate more active growth. As a result, the larvae consume their limited nutrient reserves faster and die of starvation. This could explain the longer duration of our patient's infection in New York.

A number of treatments are curative, including oral thiabendazole, topical thiabendazole, and oral ivermectin. Topical thiabendazole is an effective treatment without the side effects of oral thiabendazole (10, 11). Our patient was treated with a topical 15% thiabendazole cream two to three times a day and responded with dramatic relief of pruritus within 24 hours.

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Student Corner

Intussusception in Adults

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Abstract

Intussusception in adults is a rare entity that it is generally caused by definable intraluminal pathology. We report four cases of adult intussusception caused by lymphoma of the terminal ileum (2), an inflamed appendix (1) and a mucosal polyp (1). All presented with a variety of nonspecific and chronic symptoms, including abdominal pain, nausea and vomiting, consistent with partial small bowel obstruction. Only one patient had palpable masses in the abdomen. The most useful diagnostic radiological method was computed tomography (CT), which showed "target" lesions. The presence of the characteristic "target" lesion may obviate the need for further studies, including a barium enema. As in the cases reported here, treatment involves more than simple reduction; surgical resection is usually indicated. **Key Words:** Intussusception, small bowel obstruction, barium enema.

Introduction

Intussusception, although common in the pediatric population, is rare in adults. It occurs when a proximal segment of intestine (intussusceptum) telescopes into the intestinal segment distal to it (intussuscipiens) (1). The most common sites of occurrence are the junctions between the freely moving segments of the bowel and segments that are relatively fixed, either due to their retroperitoneal location or to adhesions. Examples include ileocolic, colocolonic, and enteroenteral intussusception (2).

Adult intussusception is associated with a definable pathologic lesion or lead point in 70–90% of cases (1, 3–5). Intraluminal lesions alter normal bowel peristalsis and form lead points for the intussusceptum (6, 7). Adult intussusception presents with a variety of acute, intermittent and chronic symptoms mimicking partial small bowel obstruction. Preoperative diagnosis is often difficult to establish. Computed tomography (CT) has proven useful in establishing the diagnosis; however, diagnosis is most often established at surgery. Treatment involves surgical resection of the involved segment of the bowel, as intraluminal pathology is present in most cases. Whether reduction should be performed prior to resection remains controversial (2).

Four cases of adult intussusception are reported. All patients were male, with ages ranging from 26 to 44 (Table 1).

Case 1

A 26-year-old, otherwise healthy male reported to the emergency room with the complaint of intermittent, "crampy" midepigastric and right lower quadrant abdominal pain of two weeks' duration. The abdominal pain, which had been increasing in intensity, was not associated

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TABLE 1
Summary of Patient Symptoms, Etiologies, and Treatment

Case	Age	Symptoms	Location	Cause	Treatment
1	26	Midepigastric/RLQ pain	Ileocolic	Malignant B cell lymphoma	Ileocolic resection
2	44	RLQ pain Bloody stools	Ileocolic	Large B cell lymphoma	Right hemicolectomy
3	41	RLQ pain Guaiac positive	Ileocolic	Chronic appendicitis	Ileocolic resection
4	44	Diffuse abdominal pain	Ileojejunal	Mucosal polyp	Small bowel resection

with nausea, vomiting or diarrhea, but was aggravated by spicy foods.

Physical examination revealed normal bowel sounds, and tenderness in the right lower quadrant; a slight fullness was palpable in this region. The patient's rectal examination revealed no masses and a stool guaiac test was negative. Laboratory studies were normal. An abdominal ultrasound was performed which demonstrated a normal gallbladder without evidence of cholelithiasis. However, a dense mass was present in the right lower quadrant. Computed tomography (CT) identified a "target" lesion in this region that had the characteristic appearance of intussusception (Fig. 1). Barium enema subsequently revealed the presence of intussusception of the terminal ileum into the ascending colon (Fig. 2).

The diagnosis was confirmed intraoperatively, and a laparascopic-assisted ileocolic resection was performed. Examination of the surgical specimen confirmed an intussusception of the terminal ileum into the ascending colon, with a significant amount of surrounding inflammation (Fig. 3). Reduction of the intussusception was not possible. Final pathology demonstrated B cell lymphoma with transmural involvement.

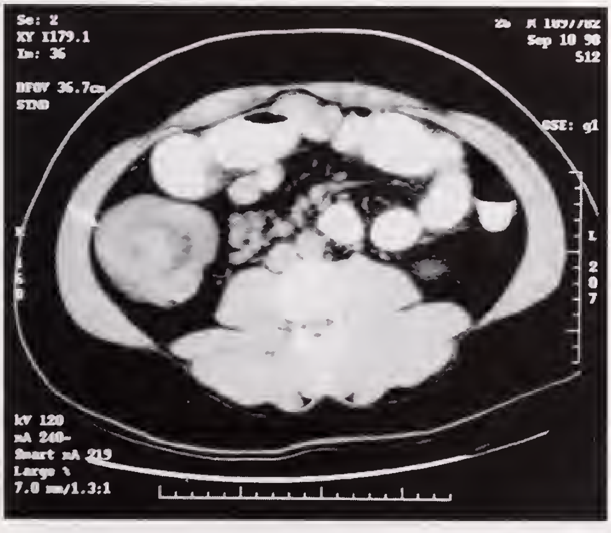

Fig. 1. Case 1: Computed tomography scan. Arrow indicates target lesion in ileocolic region.

Case 2

A 44-year-old male with AIDS presented to the emergency room with complaints of severe, crampy right lower quadrant abdominal pain for two weeks. The pain was continuous with frequent exacerbations, but was not associated with nausea, vomiting or diarrhea. The patient also reported an episode of bloody stools two days prior to his presentation.

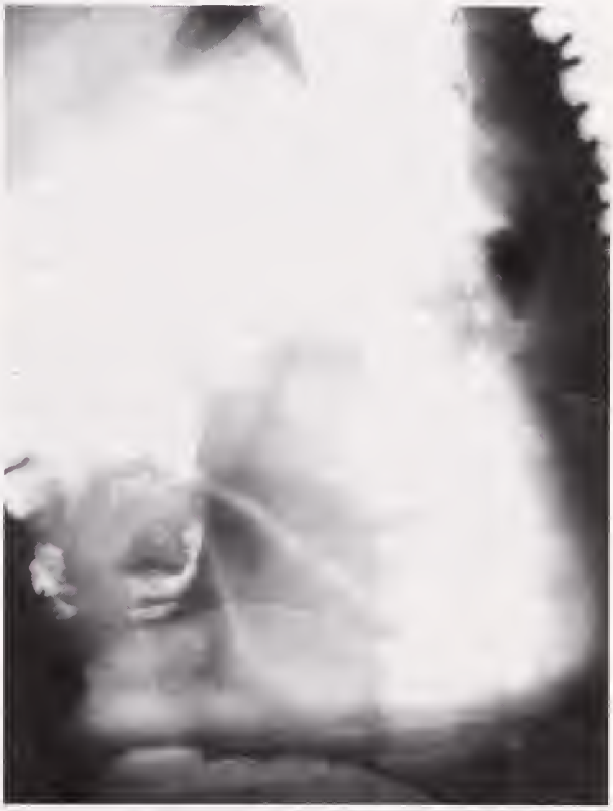

Fig. 2. Case 1: Barium enema revealing intussusception.

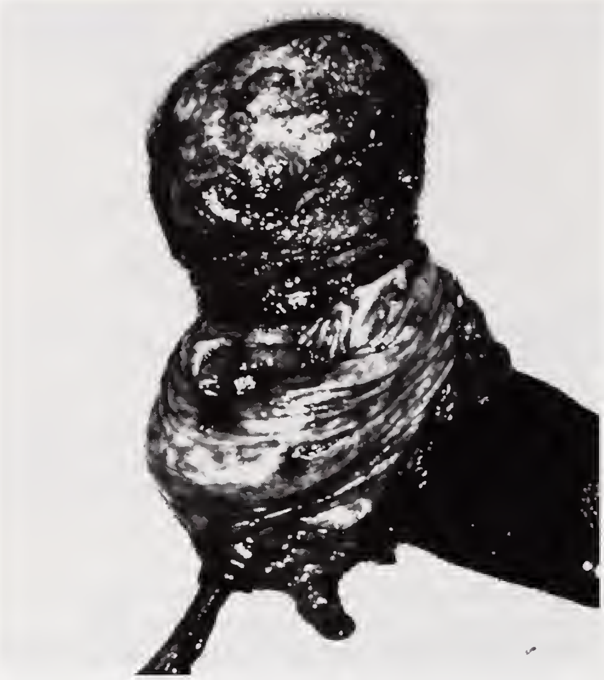

Fig. 3. Case 1: Surgical specimen revealing ileocolic intussusception.

On physical examination, he was afebrile with normal vital signs. His abdomen was soft and non-distended, with normal active bowel sounds. A slight fullness was noted in the right lower quadrant, which was tender on deep palpation. There was no rebound tenderness or guarding. Rectal examination was negative except for guaiac positive stools. Sonography revealed a mass in the right lower quadrant. A CT scan of the abdomen demonstrated the presence of a large cecal mass, which was subsequently confirmed by barium enema. Colonoscopy revealed a large submucosal mass in the cecum; a biopsy demonstrated acute and chronic inflammation.

Laparotomy confirmed the diagnosis of an ileocolic intussusception. A tumor in the terminal ileum was the cause of the intussusception. Multiple nodes were present in the mesentery and the appendix was found to be normal. No attempt was made to reduce the intussusception prior to performing a right hemicolectomy. Pathological examination revealed B cell lymphoma.

Case 3

A 41-year-old male with no significant past medical or surgical history presented to the emergency room with a 6-month history of intermittent, non-radiating, right lower quadrant abdominal pain. When the abdominal pain persisted for more than 24 hours, he came to the emergency room. He did not complain of nausea, but had vomited once and was slightly febrile. He also complained of constipation for two days and anorexia for one day.

On physical examination, the patient was afebrile with normal vital signs. Abdominal examination revealed a mildly tender right lower quadrant. There was no rebound tenderness or guarding. There was a palpable mass in the right lower quadrant. Rectal examination revealed no tenderness or palpable masses; however, stool guaiac was positive. Laboratory examinations were normal. An obstructive series revealed a single dilated loop of small bowel with air fluid levels. A CT scan demonstrated intussusception of the ileocolic region, with a "target" lesion in the right lower quadrant. An ileocolic resection was performed. Reduction was not attempted prior to resection. Examination of the specimen revealed an ileocolic intussusception with the appendix as the lead point. Pathological examination demonstrated an acutely inflamed appendix with signs of chronic inflammation (Fig. 4).

Case 4

A 44-year-old male with no significant past medical or surgical history presented with a two-month history of intermittent, diffuse abdominal pain. Just prior to admission he had developed acute abdominal pain associated with some swelling of the right side of his abdomen. Associated symptoms included nausea, three episodes of vomiting, and constipation.

Physical examination revealed mild abdominal distention, normal bowel sounds, and tenderness in all four quadrants. Rebound tenderness without guarding was present in the right lower

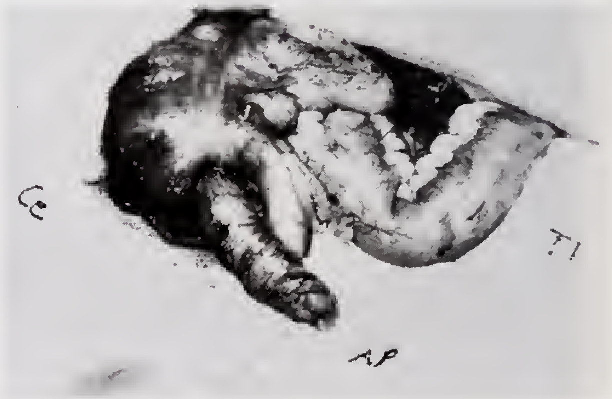

Fig. 4. Case 3: Surgical specimen demonstrating inflamed appendix and ileocolic intussusception.

quadrant. Rectal examination revealed no palpable masses or tenderness and guaiac negative stools. His white cell count was 12,000/mm^3. Blood chemistries and liver function tests were within normal limits. An obstructive series demonstrated evidence of small bowel obstruction, which was subsequently confirmed by abdominal CT scan. CT scan demonstrated a mass consistent with intussusception (Fig. 5).

At laparotomy, a jejunoileal intussusception was found and a small bowel resection was performed. Examination of the surgical specimen demonstrated a gangrenous, intussuscepted loop of distal jejunum into the proximal ileum. Pathology revealed a mucosal polyp with near total infarction. The lesion appeared benign. The exact nature could not be determined due to extensive necrosis.

Discussion

While relatively common in the pediatric population, intussusception is a rare entity in adults and accounts for one percent of bowel obstructions (4). Its clinical presentation is generally nonspecific and chronic, and includes abdominal pain with or without associated nausea and vomiting. The predominant symptoms are usually those of bowel obstruction; consequently, misdiagnosis is common at presentation (1, 8). Abdominal mass, gastrointestinal bleeding and acute cholecystitis follow in frequency as incorrect preoperative diagnoses (1).

The predominant symptoms in our series were consistent with those of partial small bowel obstruction; three of four patients presented with nausea, vomiting, and abdominal pain. Similarly, other series report pain as the most common presenting symptom (71–90%), with vomiting and red blood per rectum following in order of frequency (5). The most consistent characteristic of the pain is its periodic and intermittent nature (2, 5, 7, 9, 10). In a recent review of 54 cases of intussusception, patients with benign lesions typically presented with nausea, vomiting and abdominal pain, while those with malignant etiologies more often presented with melena and guaiac positive stools (1). Other series have demonstrated a palpable mass in 24–42% of cases (7, 10).

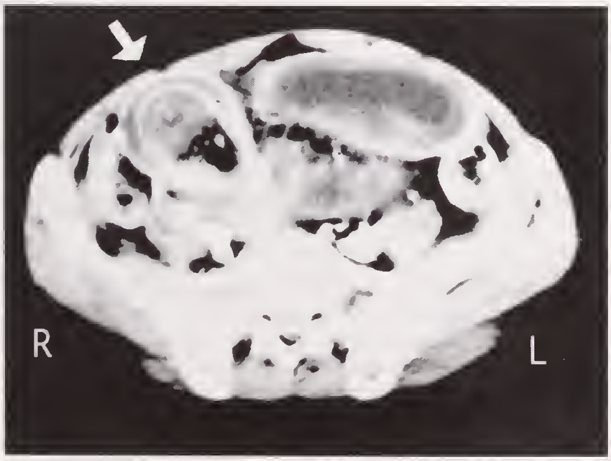

Fig. 5. Case 4: Computed tomography scan. Arrow indicates target lesion.

A number of radiological studies may be useful in the preoperative diagnosis of intussusception, although the varied symptomatology renders it difficult to describe the perfect diagnostic algorithm (1). Various authors have advocated the use of CT scans, barium studies, abdominal ultrasound, plain film, and radionucleotide studies (11–13). However, a correct preoperative diagnosis is established in only 32% of patients with intussusception (1).

In cases in which the clinical picture involves obstructive symptoms, plain abdominal films may help in identifying the site of intussusception. Ultrasonography has also proved accurate in diagnosing intussusception in children and adults (14). In one series, 145 cases of childhood intussusceptions were diagnosed by ultrasound (14). However, its diagnostic value is limited in evaluation of acute obstructive symptoms, as air in the bowel typically results in poor signal transmission (2). Contrast study, in particular barium enema, utilized as both diagnostic test and as therapeutic modality in children, adds little to the evaluation in the adult, once computed tomography is performed.

In our own series, CT scans proved to be most valuable in preoperative diagnosis. CT scans identified an obstructing lesion in all four patients, and in three, the characteristic "target" lesion was present. Our results are consistent with a recent report by Azar et al. in which abdominal CT scan provided correct diagnoses in 78% of cases (1). "Target" masses, although not pathognomonic, can be demonstrated on CT and ultrasound (11–13). The intussusceptum is the center of the target lesion and the edematous intussuscipiens forms the external ring (1). In our series, a subsequent barium enema was performed in two cases to confirm the diagnosis. However, this study may be unnecessary in adult cases. The diagnostic algorithm for adult intussusception may require only abdominal plain films and CT scan before surgical intervention.

Three out of the four cases reported here involved the ileocolic region. In one study that reviewed 677 cases of adult intussusception, 53% arose in the duodenum, jejunum or ileum. Of these cases, 14% had a lead point at the ileocecal valve, 16% were colonic lesions, and approximately 5% involved the appendix (15). More recent studies confirm the finding that the majority of lesions arise in the small bowel and that ileocolic, colonic, and appendiceal intussusception are rare (2, 5, 16).

In our series, all four patients presented with a demonstrable lead point. The two malignant lesions were lymphomas, both involving the ileum. The remaining two lesions were benign and included a small bowel mucosal polyp and an inflamed appendix. In Azar's study, 52% of small bowel intussusception were caused by benign conditions. The benign lead points included postoperative adhesions or suture lines of previous anastomoses. Other causes included Meckel's diverticulum, benign neoplasms and inflammatory lesions. Malignant lead points in the small bowel are usually metastatic lesions.

For colonic intussusception, the percentage of malignant lesions varies. Some series demonstrate that approximately 50% are malignant (5, 17). In one study, which reviewed 350 cases of colonic intussusceptions, 68% had malignant lead point with adenocarcinoma of the colon accounting for 62% of these lesions (18). More recent, smaller studies show similar frequencies, with two-thirds of intussusceptions due to malignancy (7, 16). The appendix as a lead point is rare, with only 200 cases reported in the literature (2, 19, 20).

The treatment of adult intussusception remains controversial. All authors agree that resection is necessary, as a pathologic lesion, possibly malignant in nature, is usually present (2, 6, 18). However, a question remains regarding the role of reduction prior to resection. Due to the high incidence of malignancy in adult intussusception, especially in those cases involving the colon, reduction may result in transperitoneal seeding. Resection without reduction allows uninjured bowel to be used in the anastomosis (2) and avoids spillage of bowel content if inadvertent perforation would otherwise occur.

While many early reports advocate reducing the intussusception prior to resection, more recent reports have advocated selective reduction before resection (5, 16). In cases of benign small bowel lesions, such as postoperative adhesions, intraoperative reduction is acceptable if the bowel is viable (5, 6). In patients without a history of previous laparotomy, resection without reduction is advocated, due to the high risk of malignancy (1). Also, in cases in which the bowel is inflamed or ischemic or in cases of colonic intussusceptions, resection without attempt at reduction is advised in order to avoid inadvertent perforation of the bowel and tumor seeding (1, 2).

Adult intussusception is a rare entity with no uniform presenting symptoms. Consequently, its diagnosis may be challenging. It typically presents with a variety of nonspecific and chronic symptoms that include abdominal pain, nausea, and vomiting. The most useful diagnostic radiological method is the CT scan. The presence of the characteristic "target" lesion may obviate the need for further studies, including a subsequent barium enema. Usually, there is a definable lead point in adult cases, and resection of the involved bowel, not simple reduction, is indicated.

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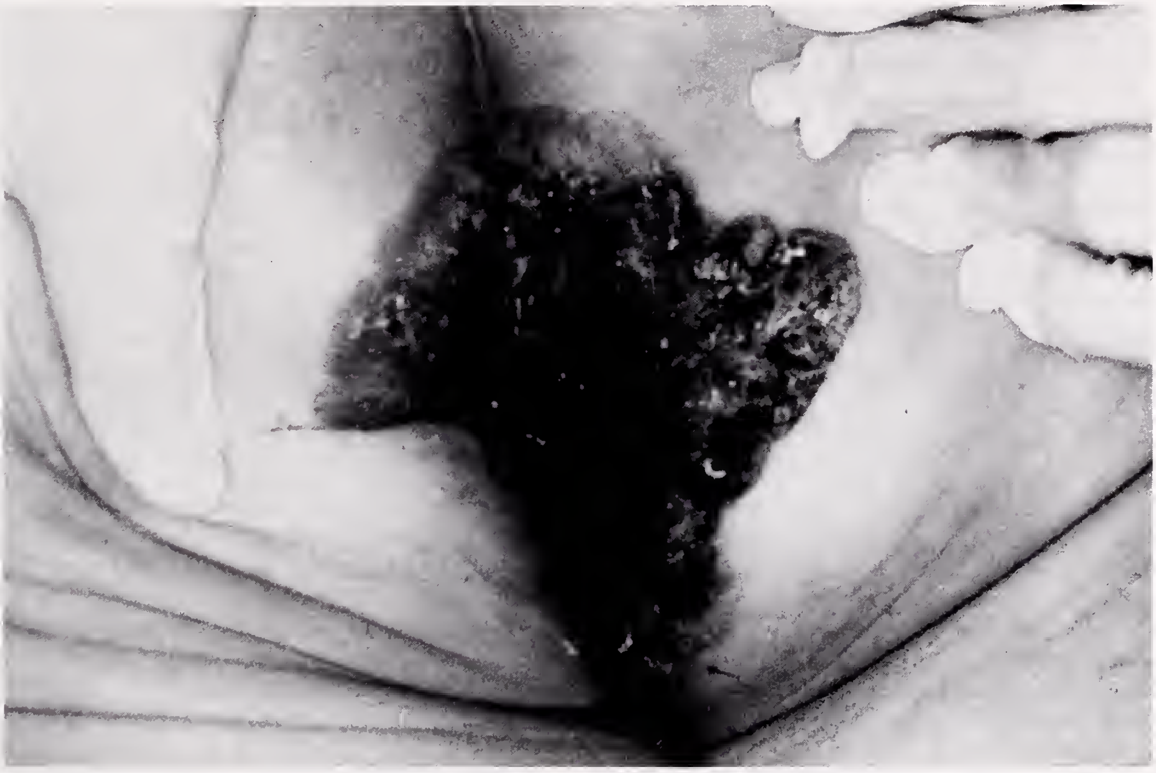
Dermatology Notes

Extramammary Paget's Disease



THIS ULCERATED PLAQUE had been present in the perianal area for several years. In its early stages, extramammary Paget's disease can be mistaken for psoriasis, intertrigo, or fungal infection. This tumor is locally invasive and has potential for metastasis. It occasionally arises in association with an adenocarcinoma of underlying secretory glands or may be associated with a primary adenocarcinoma of the rectum, urethra, or cervix.

—Jacob Baral, M.D. and Mark Lebwohl, M.D.

Editor's Note

Sherman Kupfer, M.D.

With this issue, *The Journal* will begin to republish some of its classic articles which have been judged to have reported important scientific contributions. These articles still are available in hard copy format and can be obtained from medical libraries in which *The Journal* has been maintained. However, the advent of the web and electronic publishing has made it possible to present the most recently published articles in a most convenient manner to a much wider audience in all corners of the world. In addition, and unfortunately for the time being, since the information in the National Library of Medicine database only goes back to circa 1965, the retrieval of earlier information must be done the old-fashioned way. That is not to say that the old-fashioned way is bad, but it is cumbersome and time consuming. For these reasons, the effort is rarely made, and citations of articles of this vintage often derive from other than the primary source. This is a shame since authors of recent articles often miss the beauty in this early prose and in the nuances and speculations presented by those who struggled with the then, by today's standards, inadequate techniques. Progress in science is built on what has gone on before, even before 1965, and we need not apologize for what has been reported as fact and truth and which ultimately turned out to be erroneous. Such mistakes often have galvanized the quest to disprove the old truths and find new ones. *The Journal* has played its reportorial role in this endeavor and is very much eager to continue to do so with the new techniques available to it.

The initial article to be revisited appeared in the very first issue of *Journal of The Mount Sinai Hospital* in 1934 – 1935 and was authored by James B. Collip. This presentation was made over a two-day period as the opening lecture of a series dedicated to William H. Welch. Welch was a very good and close friend of Emanuel Libman who died in 1946, and who was, and still is, considered to be one of Mount Sinai's most famous clinicians of any era. Welch was born in 1850 and died in 1934, about one month after this lecture was given. He was a trained pathologist who was instrumental in the rise of the medical school at Johns Hopkins University in Baltimore at the end of the 19th century. He played a major role in the introduction of the revised medical curriculum which led to modern concepts of medical education and practice. He was dean at that school from 1893 – 1898.

Welch's initial graduate medical studies began in the laboratory of Julius Conheim of the University of Breslau where he witnessed Koch's demonstration of the infectivity of *Bacillus anthracis*. He returned to the United States in 1879 and assumed the position of professor of pathology and anatomy at Bellevue Hospital Medical College. Five years later, he went to Hopkins as Chairman and Professor of Pathology. He was instrumental in recruiting Osler to the Hopkins faculty.

Welch is best known for his work with Simon Flexner on the pathological effects of diphtheria toxin and for his demonstration of *Micrococcus albus* and its role in wound infection. As an aside, in 1923, Bela Schick, who had earlier described the test to determine which children were susceptible to the scourge of diphtheria, became Pediatrician to The Mount Sinai Hospital. Welch also discovered *Clostridium welchii* as the cause of gas gangrene. In later years, he became director of the Johns Hopkins School of Hygiene and Public Health and the medical school's first professor of the history of medicine. It is clear that Libman at Mount Sinai, and Welch at Hopkins, had much in common. It was, therefore, fitting indeed that Mount Sinai honor Welch with a named lecture series which continued for many years.

Collip, a well-known scientist and medical educator, was trained at the University of Toronto in biochemistry. He became Professor of Biochemistry at the University of Alberta in 1922, and then at McGill University in 1928. He was appointed Gilman Professor of Endocrinology and Director of the Research Institute of Endocrinology at McGill in 1941. He went on to become Dean of Medicine and Professor and Head of the Department of Medical Research at the University of Western Ontario in 1947. He retired as dean in 1961.

Collip wrote extensively on blood and tissue chemistry and the internal secretions of insulin, parathyroid hormone, placental hormones, and pituitary hormones. In his lecture at Mount Sinai delivered in 1934, he presented much of the experimental findings observed by many of his students and other individuals whose names are legends to those cognoscenti in the field of the "master gland." However, many of the terms he used have changed over the course of time as new information became available. It is clear that the cycle of bedside observations and laboratory bench research and vice versa was of paramount interest, even at that time. It is of interest to reflect on how radioimmunoassay technology revolutionized endocrinology specifically, and many other fields as well. For all of these reasons, some admittedly implicit, it is my hope that the readers of *The Journal*, as successor to the original publication called *Journal of The Mount Sinai Hospital*, will find that this effort at highlighting some history at Mount Sinai will prove to be useful, stimulating if not provocative, and worthwhile.

The William Henry Welch Lectures

Some Recent Advances in the Physiology of the Anterior Pituitary[1]

J. B. Collip, M.D., F.R.S.

The history of pituitary physiology has passed through various stages. The earliest period in the development of our knowledge on the functions of this gland is that of the anatomists. In this era pure morphological observation and theoretical speculation were the only means by which scientists tried to attack these problems, and the results they obtained would certainly seem rather ingenuous today. First Galen (1) thought the function of the gland to be filtration of a mucous fluid produced by the brain and its secretion into the nasopharynx. Therefore he called the gland "glandula pituitaria." Piccolhomini (2), in 1636, maintained that the function of the pituitary is to close the lower aperture of the infundibulum, and thus to prevent the spirits of life from escaping.

The next period in the history of pituitary physiology was that of clinical observation of hypophyseal diseases initiated by Pierre Marie's classical papers on acromegaly. These observations first called attention to the role of this gland in the regulation of somatic growth.

The modern era in the study of this gland began with the introduction of experimental methods. Just as in the study of other endocrine glands, it has been of great value to observe the changes following the removal of the pituitary from the organism. This operation, which was first performed by Sir Victor Horsley in 1886 (3), has proved to be of great assistance in the solution of problems concerning pituitary physiology. The technical difficulties connected with it account for the poor results of earlier workers, which led to erroneous conclusions. Most of their experimental animals died shortly after removal of the gland and therefore they concluded (Vassale and Sacchi (4); Biedl (5) and others) that the hypophysis is absolutely essential for life. Improvements of the surgical method by later investigators such as Cushing, Aschner, Smith and others have now definitely established the fact that an animal may live for very long periods after complete hypophysectomy.

By far the most satisfactory approach is the oral, or parapharyngeal route, which allows the removal of the gland without injury to the adjacent hypothalamic centres of the brain. This method has been used throughout in our laboratory and enabled us to study, during the past two years, the effects of hypophysectomy on mice, rats, guinea-pigs, cats, dogs and monkeys.[2] We found it very helpful to use ether as an anaesthetic, given through a tracheal cannula, or an intratracheal tube. The danger of meningitis is comparatively slight, even though an open communication is left between the sella turcica and the nasopharynx, for this communication is closed very soon after operation by a clot.

I should like to give you now a short description of the symptoms of pituitary deficiency which appear after surgical removal of the gland, and also of the effect of replacement therapy.

GROWTH

In accordance with observations of other investigators, we can confirm the observation that removal of the pituitary stops growth, but we found that there is one rather remarkable excep-

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[1] Delivered at The Mount Sinai Hospital, New York City, on March 26 and 27, 1934. Reprinted from Vol 1:28–71. 1934.

[2] Doctor Hans Selye has carried out most of the hypophysectomies.

tion to this rule. If hypophysectomy is performed in very young animals for instance, in rats about three weeks of age, growth does not stop immediately after operation, even though the gland is completely removed. Thus we have seen that rats which weighed approximately 25–35 grams at the time of operation proceeded to grow until they reached a weight of approximately 60 grams (6). Serial sections proved that no trace of pituitary tissue was left behind. The possibility of growth in the absence of pituitary tissue in very immature animals is of particular interest, because it shows that in early stages of ontogenetic development the organism must have an extrahypophyseal source of growth-stimulating substances. Here again we see once more the striking parallelism between ontogenetic and phylogenetic development, for it has been shown that the growth in length of reptiles and amphibia is also largely independent of the pituitary and therefore will not be completely inhibited by hypophysectomy.

The most satisfactory test animal for the standardization of hypophyseal growth hormone has proved to be the hypophysectomized rat of about 100 grams in weight. If the pituitary is removed at this period, growth will stop immediately unless growth-hormone-containing extracts are administered.

Physiological effects of the growth hormone

Hypophysectomized rats treated with a purified growth hormone (Q extract) put on weight immediately. This is in marked contrast to the effect which we obtained in our earlier work when crude alkaline extracts of anterior lobe were being used. We observed then that a period of about ten days elapsed before any appreciable growth took place. This we know now was due to the presence of the thyreotropic principle in the extracts used at that time, since simultaneous administration of the purified growth and thyreotropic principles does not result in growth until late in the second week. This apparent inhibitory action of the thyreotropic substance upon the growth substance is due probably to the increased metabolism offsetting the growth effect and is not a direct antagonistic action of the thyreotropic and growth principles. We agree with Evans that adult rats whose growth curves are plateaued may be caused to grow with the growth extract. We have been unable to affect appreciably the growth curve of normal male rats treated daily with the Q extract from the 4th week of life. Female animals so treated do show some acceleration of their growth rates as compared with their controls.

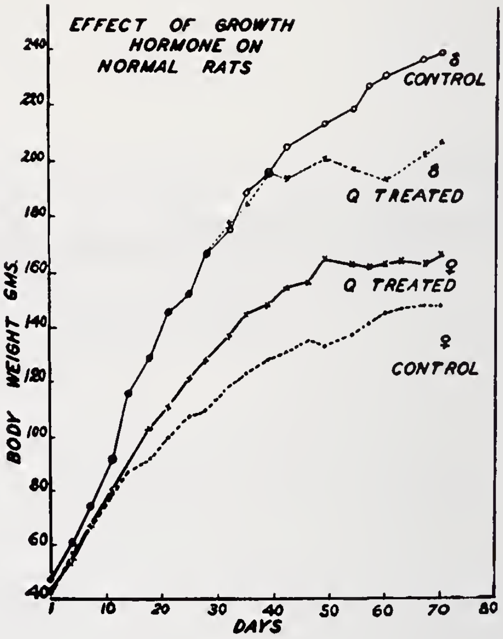


Chart 1. Growth curves of normal rats treated with growth hormone (Q extract) compared with untreated controls, male and female. Note the positive effect in the treated females (see Evans).

Hypophysectomized rats treated with the Q extract have been caused to increase their weight at the rate of about 2–3 grams per day for 35 days. This rate of growth cannot be maintained, however, and in the course of some weeks they cease to grow and may actually lose weight in spite of continuous treatment with a known potent extract.

Hypophysectomized rats treated with Q extract show in addition to actual increase in body weight a very definite change in their nitrogen and calcium metabolism. The nitrogen balance changes from a negative to a positive one, as shown by the studies of Mr. Peter Black, and the calcium balance is influenced in the same direction, as has been shown just recently by Dr. Leonard Pugsley. Skiagrams of the skull made under especially devised and controlled conditions in our laboratory by a guest worker, Dr. Hector Mortimer, show clearly that the Q extract produces very marked changes. The failure of growth of the cancellous elements in the hypophysectomized animal is not only made good, but in certain cases these structures may even become hyperplastic by the suitable exhibition of Q extract.

Chemistry of the growth hormone

The alkaline extract of anterior lobes first described by Evans is very rich in the growth hor-

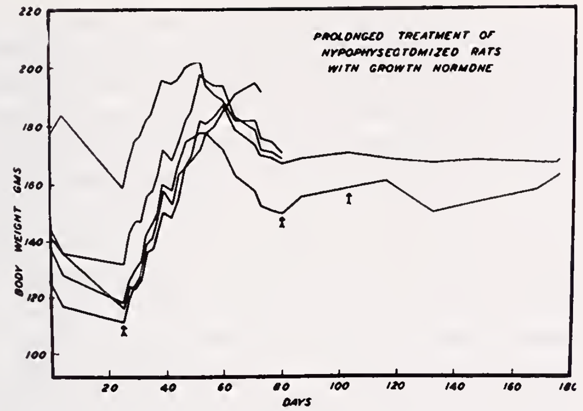


Chart 2. Growth curves of hypophysectomized rats treated with Q extract and fed on adequate diet. Note development of resistance after about 35 days of treatment.

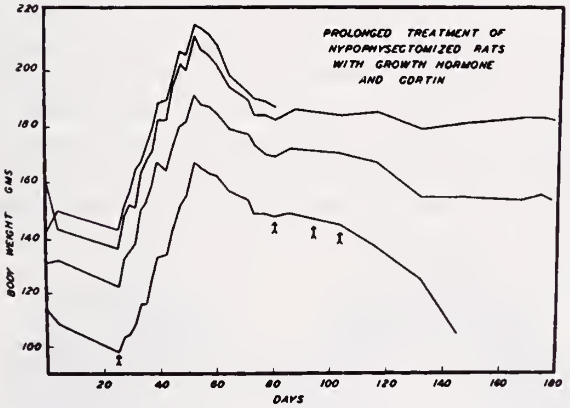


Chart 3. Like Chart 2, but illustrating non-effect of cortin.

mone. It contains so much of the other pituitary principles, both active and inert, that an attempt was made to prepare an extract from which as much as possible of these contaminating substances would be removed, at the same time leaving the growth hormone in an active state. Many methods have been tried. It is possible to obtain potent extracts of the growth principle by a variety of procedures, such as extraction of the acetone-dehydrated fresh lobes with either aqueous alkaline or aqueous-acid media, or acid-acetone or alcohol of 60 per cent concentration, followed by subsequent fractionation with salt, alcohol and acetone, and isoelectric precipitation. If one is desirous of obtaining a relatively pure hormone extract rather than quantitative recovery of the total active principle present in the original gland tissue, the following method may be employed (8).

Desiccated acetone-dehydrated anterior lobes of cattle are ground to a pulp and suspended in ten volumes of distilled water. The mixture is vigorously stirred and then is made alkaline to the extent of 0.25 per cent NaOH by the addition of the requisite amount of a saturated aqueous solution. The mixture is allowed to stand for two hours. This preliminary treatment with dilute alkali serves a twofold purpose: (1) destruction of any contaminating posterior lobe principles, and (2) facilitating solution of the tissue. Also, the mild hydrolytic action of the dilute alkali is probably of definite value.

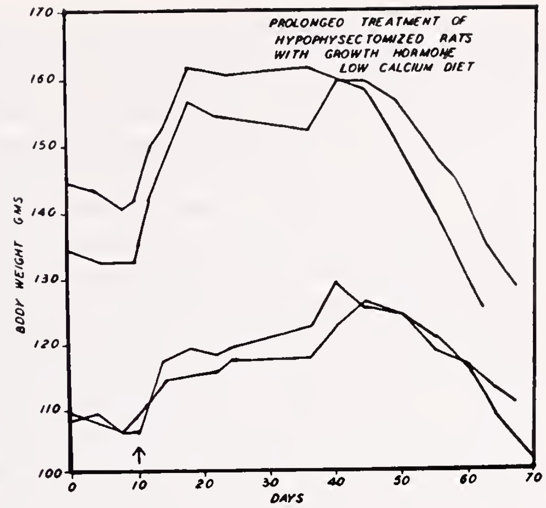


Chart 4. Growth curves of hypophysectomized rats treated with extract and fed a low calcium diet. Note the rapid loss in weight after resistance has developed.

The alkaline mixture is treated next with sufficient acetic acid to give a marked flocculation (isoelectric precipitation of the proteins). The pH

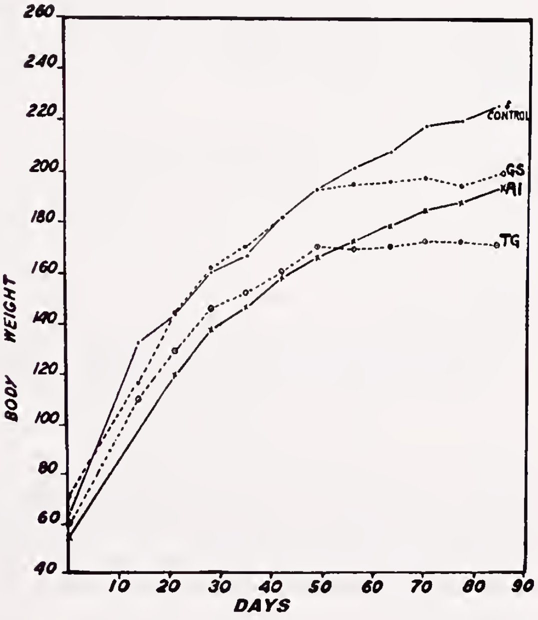


Chart 5. Growth curves of normal male rats treated with: T.G.–thyreotropic hormone; A.I.–adrenotropic hormone; G.S.–a mixture of anterior lobe principles. Note that prolonged treatment with pituitary principles definitely slows the growth rate.

should be about 5.5. Under these conditions filtration of the mixture can be carried out quite rapidly. The residues are suspended in ten volumes of distilled water; the mixture is made alkaline (0.1 per cent NaOH) and again precipitated at the isoelectric point as in the first instance. After filtration the residues are again treated as above, and for a thorough extraction of the gland tissue this part of the process should be repeated five times. The combined filtrates are concentrated at low temperature and pressure to 1/25 to 1/50 the original volume. The concentrate contains the growth hormone, which tends to precipitate out as an isoelectric protein fraction during the concentration process; the thyreotropic hormone; the adrenotropic hormone; a maturity factor; some prolactin; a ketogenic and a diabetogenic substance. Both of these latter may not be definite entities, as will be seen in the subsequent discussion.

A very satisfactory growth hormone preparation can be obtained by filtering off the flocculence which appears as a result of the vacuum distillation. This precipitate should be dissolved in 0.1 per cent NaOH and reprecipitated at the isoelectric point by careful addition of dilute acetic acid. Flocculation of the isoelectric precipitate is aided by further concentration of the mixture at low temperature and pressure. This protein-like fraction should be further purified by repeated isoelectric precipitation.

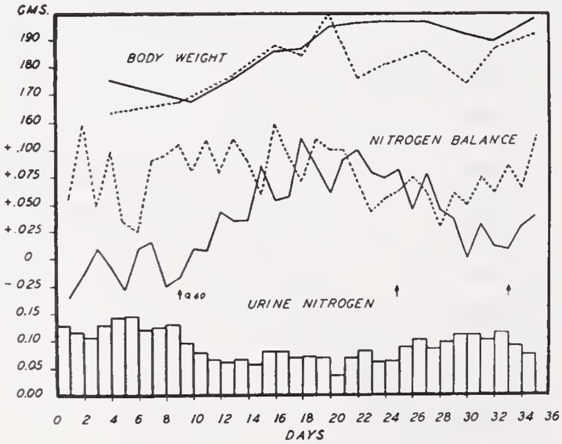


Chart 6. Showing the effect of the growth hormone upon growth, nitrogen balance and urinary nitrogen of completely hypophysectomized rats (solid line) and of normal animals (dotted line). At the first arrow the injections were started; at the second, injections were stopped; and at the third, they were started again.

The filtrates obtained in this process are combined and worked up for the thyreotropic and adrenotropic active principles (9, 10).

The best growth hormone preparations are made by treating the concentrate of the combined original filtrates with $Ca_3(PO_4)_2$ in the presence of 1 per cent ammonia (8). The suspension of calcium phosphate in the concentrate is best produced by adding separately, during vigorous agitation, $CaCl_2$ and NaH_2PO_4 in appropriate amounts. Agitation of the mixture is maintained by further concentration in the vacuum still. The mixture is filtered and the filtrate is washed with dilute ammonia water (0.05 per cent) until the filtrate is colorless. The $Ca_3(PO_4)_2$ mass is suspended in water and made alkaline with NaOH (0.5 per cent). The mixture is filtered and the whole process is repeated three times. The combined filtrates are neutralized with acetic pH 6 and concentrated at low temperature and pressure to a small volume. The precipitate is removed by filtration and after solution in dilute soda again precipitated at the isoelectric point. The solution of the precipitate in dilute alkali represents the final product. One such preparation sterilized by Berkefeld filtration at pH 9 has shown no evidence of losing its activity over a period of one year. This has been stored in a refrigerator at about 1°C.

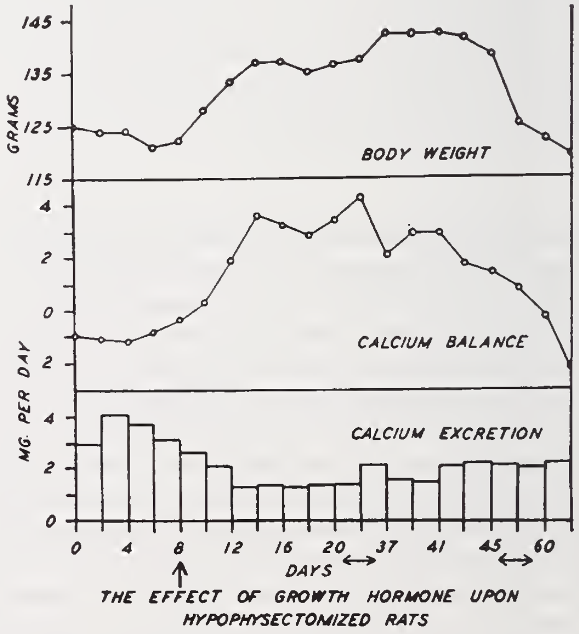
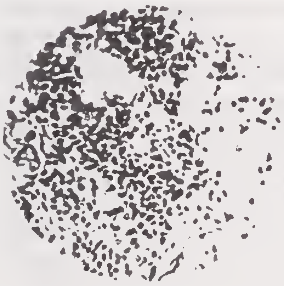


Chart 7. Showing the favorable effect of Q extract upon calcium balance in hypophysectomized rats maintained on a low calcium diet (Dr. Leonard Pugsley).

The growth hormone may be standardized by noting the growth effect upon recently hypophysectomized and otherwise untreated rats. We have taken as an arbitrary unit the amount of extract necessary, when administered twice daily by intraperitoneal injection, to cause a weight increase of 1 gram per day in 100 gram rats, over 10 to 15 days (8). Extracts made by the method outlined above may contain from 25 to 100 units per cubic centimeter representing 1 gram of original pituitary tissue.

SEX

Another important effect of hypophysectomy is the atrophy of the genital organs. The germinal epithelium of the testis atrophies and sperm cell formation stops. In the ovary follicle maturation and corpus luteum formation is inhibited and the animals become continuously dioestric. But the effect of the pituitary on the ovary is not limited to the maturation of follicles; in fact we have been able to show that the so-called "maturity hormone" is as important for the immature ovary as it is for the mature one. Before puberty, there is no follicle maturation, nor oestrus, nor corpus luteum. formation, but the ovaries of prepubertal hypophysectomized animals still show definite signs of hypophyseal deficiency (39).



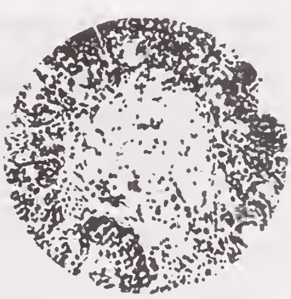


Fig. 1. Ovary of hypophysectomized rat two months after hypophysectomy. The theca cells are changed into theca-deficiency cells and their nuclei show the typical wheel shape.

Fig. 2. Involuted corpus luteum in ovary of hypophysectomized post pubertal rat 265 days after hypophysectomy.

The thecal cells, which ordinarily have a spindle-shaped nucleus and a fine granular chromatin structure, change their appearance. The nuclei become circular and their chromatin aggregates in large, dark lumps, peripherally arranged, leaving white, chromatin-free spaces in between, so that the nucleus comes to present a somewhat wheel-like appearance. In order to stress the origin and significance of these cells, we called them "theca deficiency-cells" (11). It has been possible to prepare suitable extracts, which will prevent or cure the effects of hypophysectomy on the gonad, and the study of replacement therapy has also led to some interesting findings concerning the difference between the various gonadotropic extracts. Thus we have found, in confirmation of P. E. Smith and others, that gonadotropic extracts prepared from pituitary tissue will lead to follicle maturation and corpus luteum formation in the hypophysectomized rat. In this respect the gonadotropic hormone of the pituitary differs from the anterior-pituitary-like hormone prepared from pregnancy urine or placenta (A.P.L.); in fact we have never been able to stimulate follicle maturation or corpus luteum formation in the absence of the hypophysis with A.P.L. (7, 40). It would be erroneous, however, to think that A.P.L. is quite ineffective in the hypophysectomized rat. Although its administration does not produce true corpora lutea, it leads to the luteinization of thecal cells and to the production of so-called "thecal corpora lutea." The main difference between the two types of gonadotropic hormones appears to be, therefore, that the pituitary hormone acts on the granulosa and on the theca, while A.P.L. luteinizes the theca only. In this respect our findings are not quite in accordance with those of P. E. Smith, who has obtained true corpora lutea by the administration of pregnancy urine preparations. It is interesting to note, however, that we repeated his experiments in our laboratory with commercial "antuitrin S" without being able to produce any results other than thecal luteinization (12). We have no explanation to offer for this discrepancy, except possibly that the "antuitrin S" used by Dr. Smith–which, as he told us, was a special preparation–was different from the commercial "antuitrin S." The difference in the morphogenetic effect of the two gonadotropic hormones is not the only one, for it has been possible to show that A.P.L. leads to continuous oestrus in the hypophysectomized adult female, while this is not the case after administration of the pituitary extract. In the case of the immature hypophysectomized female, oestrus has not been obtained after A.P.L. administration, although the thecal luteinization was very marked. These observations led to more detailed study of the effects of hypophysectomy and hypophyseal hormones on the theca cell.

The theca deficiency-cells, as described above, can easily be brought back to normal by the administration of A.P.L.; in fact, we have seen that they may be stimulated to such a degree as to take on the appearance of corpus luteum cells. The confinement of A.P.L. action to the theca cells is observed not only in the hypophysectomized animal but also in the very immature rat. Administration of A.P.L. to these during the first days of life results in thecal luteinization. It is generally known that rats under 14 days of age are not suitable for the Aschheim-Zondek reaction, for they will not form corpora lutea under the influence of pregnancy urine. An histological study of ovaries of such animals, showed, however, that their gonads are by no means insensitive to A.P.L. The only difference between the somewhat older rat and the very immature animal is that the former reacts with corpus luteum formation, while the latter with the formation of thecal corpora (13). These observations led us to the conclusion that the pituitary of the very immature rat is probably not fully functional, and that this accounts for the fact that it reacts to A.P.L. in the same way as the hypophysectomized older animal.

The conclusion which we drew from all these experiments was that A.P.L. needs a complementary factor produced by the pituitary in order to act on the granulosa cell, while its effect on the theca is not necessarily dependent upon the pituitary (14, 15). This conception has also been substantiated by other experimental series, in which we found that continuous administration of A.P.L. leads to an enlargement of the pituitary and of the thyroid, as well as to development of the mammary gland to the stage corresponding to that of late pregnancy (16, 17).

The preparation of extracts containing the maturity principle of the anterior lobe

The preparation of even a relatively pure maturity hormone extract of the anterior pituitary has not yet been accomplished. There are more difficulties to be overcome in relation to the purification of this principle than in the case of any other. The great variation in the yield of active principle seen in the glands of different species is of especial interest. In our hands ox glands have been quite unsatisfactory as a source of potent extracts, whereas glands of sheep and hogs have been found to be relatively very rich in maturity principles. Others have had a similar experience in their work on pituitary gonadotropic hormones. If frozen rat pituitary glands are implanted into immature females, the gonadotropic effect is only a fraction of that obtained when fresh glands are implanted in a similar manner. Since an alkaline extract of the anterior lobes of the ox has been shown to be capable of neutralizing the oestrus effect of a potent alkaline extract of the rat's pituitary when both are administered simultaneously to the immature rat, one must recognize the existence of inhibitory substances of either a specific or non-specific nature in the fresh glands and accept as a possibility that a negative gonadotropic effect of a certain extract may be due not to absence of a maturity factor but to an inhibitory substance neutralizing the effect of an oestrogenic factor. We have frequently failed to obtain any vaginal oestrus reaction with certain pituitary extracts which have produced a definite A.P.L. ovary in immature rats. Methods of preparing gonad stimulating extracts of the anterior pituitary have been published by Van Dyke and Wallen Lawrence (18, 19, 20); Evans, Meyer and Simpson (21); Hisaw, et al. (22, 23); and others (24, 25, 26, 90).

Our best maturity extracts have been made by extracting the anterior lobes of sheep or hog with 30 per cent acetone containing 1 per cent NH_4OH. The maturity factor appears to follow the thyreotropic principle, and methods useful in purifying the latter are applicable to the purification of the former. In general these consist in isoelectric precipitation of relatively inert protein materials and concentration of the active principle by ammonium sulphate precipitation of the isoelectric filtrates, solution in water of the ammonium sulphate precipitate and precipitation from this by alcohol or acetone (70 per cent) of the active material. Salts can be removed successfully from the final extracts by dialysis. Extracts which have been made in this manner can be boiled at pH 5 for one hour without any appreciable change in the potency as regards maturity principle, whereas such treatment causes almost a complete destruction of the thyreotropic substance. This is the best evidence we have to submit that the thyreotropic and maturity factors are different substances. We do not feel, however, that it is fully adequate to settle entirely this question.

Pregnancy

In all probability the pituitary plays an important role during pregnancy. It has been possible, however, to show that hypophysectomy during the second half of pregnancy does not interfere with the maintenance of gestation. The only effect of hypophysectomy, when performed in the second half of pregnancy in rats or mice, is a marked prolongation of the gestation period (27, 28). This is most probably due to a delayed involution of the corpus luteum of pregnancy. We have found, however, in confirmation of Pencharz and Long (29), that hypophysectomy in the early stages of gestation leads to resorption of the embryos in the rat. We have been able to show that the same is true in the mouse, while the guinea-pig seems to behave differently; for we have seen that pregnancy was not interfered with in a guinea-pig hypophysectomized during a very early stage of gestation.

If the maintenance of the corpus luteum of pregnancy is not interfered with by hypophysectomy, the question arises–what is responsible for keeping this corpus luteum in a functional condition? It is very likely that the pregnant uterus itself is responsible for this, since removal of the foetuses leads to immediate involution of the corpus luteum of pregnancy. In order to determine whether the presence of the embryo as such is essential, or whether the distention of the uterine wall is the important factor, Dr. Selye (30) performed the following experiment: In a series of pregnant rats, the uterus was emptied and melted paraffin was introduced into its cavity, so as to distend it. When these rats were killed six weeks after the operation their ovaries were considerably enlarged (fig. 3) and contained a large number of corpora lutea comparable to those of pregnancy. The mammary glands, however, had completely retrogressed. It seems from this experiment that the mere distention of the uterine wall as such has a great effect upon the ovary. The involution of the mammary glands is not necessarily an indication of a deficiency in corpus luteum hormone production, since it is well known that even the continuous administration of corpus luteum hormone by injection cannot maintain the mammary gland in a fully developed condition for more than a few weeks. These experiments are insufficient to draw any definite conclusion concerning the role that uterine distention plays during pregnancy, but they certainly prove that the distention of the uterus has a marked effect on the ovary. We should be inclined to assume that this effect is also attained through a stimulation of the pituitary, since the hypophyses of our experimental animals–the uteri of which had been distended–were greatly enlarged. These experiments remind us of those performed by Loeb (31) on the guinea-pig, which showed that hysterectomy greatly prolongs the life-span of the corpus luteum in this species. Since hysterectomy has no clean-cut effect on the ovaries or the cycle in the rat, we assume that the mechanism at work after hysterectomy differs from that after uterine distention.

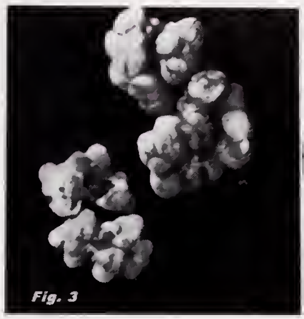


Fig. 3

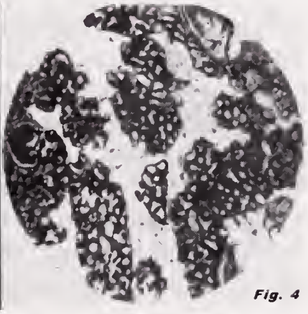


Fig. 4

Fig. 3. A pair of greatly enlarged ovaries, taken from a rat the uterus of which had been distended with paraffin, beside a pair of normal ovaries.

Fig. 4. Fully lactating mamary gland in a suckling pseudo-pregnant mouse.

Lactation

The development of the mammary gland is not interfered with (27, 32) in rats and mice hypophysectomised in the latter half of gestation. Milk secretion starts normally at parturition. This, however, lasts for but a few hours, then definitely stops. The mammary gland involutes. If hypophysectomy is performed during the course of an already established lactation, milk secretion stops within a few hours (6). As you know, it has been possible to produce a lactation-promoting hormone from the pituitary. Oscar Riddle, whose work on this subject has been of considerable importance in the elucidation of the problems of lactation and crop milk secretion, has called this hormone "prolactin." It is likely that this prolactin stimulates the secretion of the mammary gland (33, 34). Our experiments–showing that a short period of lactation may be observed soon after delivery, in animals from which the pituitary has been removed a long time before–seem to indicate that the hypophysis is not absolutely essential for the secretion of milk. There might possibly be an extra-hypophyseal source of the lactation-promoting hormone. We have considered the possibility that the pregnant uterus may also yield prolactin, and that the short lactation period observed after delivery in the hypophysectomized animal may be the result of a release of prolactin from the pregnant uterus. We know that the corpus luteum inhibits lactation, and therefore a lactation-promoting hormone would probably not lead to milk secretion during the life of the corpus luteum of pregnancy; but as soon as this corpus luteum ceases to function, lactation starts.

In this connection we performed the following experiments. A group of rats were injected with A.P.L. until their mammary glands were fully developed, and then castrated. Forty-eight hours later a histological study of the mammary glands showed that lactation had set in. In this case, the removal of the considerably luteinized ovaries initiated milk secretion in the mammary gland of the non-pregnant animal.

In another series, we treated a group of rats with A.P.L. in exactly the same manner as in the previous experiment. We then castrated them, and removed the hypophysis at the same time. Under these conditions, no milk secretion was observed. Our conclusion was that the removal of the ovary, with its corpora lutea, stimulated the secretion of prolactin from the pituitary, and thereby initiated milk secretion. If the pituitary was removed, milk secretion could not occur. If we compare the results of these experiments with those on pregnant animals, as previously described, we see that the only difference between them is the presence of a pregnant uterus. It is suggestive, therefore, to assume that this pregnant uterus was responsible for the initiation of milk secretion following parturition (17, 35).

In order to determine whether the pregnant uterus is able to produce prolactin at any time during gestation, we removed the foetuses and the pituitary simultaneously during the second part of pregnancy, and we found that Caesarian section, which ordinarily initiates milk secretion, is unable to do so in the absence of the pituitary. Animals impregnated at the postpartum cycle immediately after delivery of a litter (thus pregnant and lactating at the same time) were hypophysectomized. Milk secretion ceased immediately. Thereupon we came to the conclusion that the substance which stimulates milk secretion in the hypophysectomized animal is probably released from the pregnant uterus only shortly before parturition (36).

It is well known that weaning stops milk secretion. The explanation of earlier workers was that the accumulation of the products of secretion within leads to pressure atrophy of its epithelium, and thereby stops secretion. In the light of the "prolactin" theory, we were interested to see whether the stimulus of suckling has any direct effect on the production of prolactin in the pituitary. If this were so, one would have to assume that the mere nervous stimulus of suckling maintains milk secretion during the whole lactation period, through an effect on the prolactin production of the hypophysis. In order to test this, Dr. Selye trancised all the galactophores in lactating mice and rats while the stimulus of suckling was maintained. In this experiment no milk could escape from the gland and secretion still persisted, as long as the litter was suckling. This experiment indicates that the accumulation of milk in the gland is not the immediate cause of inhibition of secretion after weaning. In the animal from which the young have been weaned milk secretion stops because the nervous stimulus of suckling is absent (37).

The fact that the nervous stimulus of suckling has so definite an effect upon the pituitary throws an entirely new light upon the question of lactation dioestrus and lactation amenorrhoea. The fact that sexual cyclicity stops during lactation, both in experimental animals and in humans, has been interpreted as the result of the drain upon metabolism during this period. It has also been thought that it is not lactation which interferes with menstruation, but that the initiation of menstruation has an adverse effect upon lactation. In the above experiments it seems that the oestrous cycles do not appear in nursing mothers, even though the galactophores are cut. In this condition, there is no milk secretion and thus no drain on the metabolism. We thought, therefore, that the inhibition of sexual cyclicity during lactation may also be due to the nervous stimulation of suckling.

Another group of experiments was done to see whether the stimulus of suckling would also inhibit sexual cyclicity in the non-lactating animal. In a group of adult normal female rats and mice we studied the effect of the stimulus of suckling upon the oestrous cycle. We found that an adult rat, if given a litter of young animals, will build a nest and try to nurse the litter in many cases. If the mammary gland of such a rat is examined about ten days later, growing mammary epithelium is seen. At the same time the ovaries contain large corpora lutea similar to those seen during pregnancy and pseudo-pregnancy. No follicle maturation occurs and vaginal smears show continuous dioestrus. This condition is very similar to the so-called pseudo-pregnancy produced by sterile copulation or stimulation of the vagina with a glass rod. During the later stages of this pseudo-pregnancy produced by suckling, the mammary gland is well-developed and frequently numerous large placentomata are found in the uterus (figs. 4, 5). Still later, lactation sets in (Selye and McKeown (38)).

This type of pseudo-pregnancy is particularly interesting because it may have a parallelism in humans. While sterile copulation does not interfere with the cycle in women, the stimulus of suckling has a definite inhibitory influence as shown by lactation amenorrhoea. We would be inclined to interpret this condition as the result of the nervous stimulation of the nipple. These experiments may also give a more satisfactory explanation of the fabulous accounts of various investigators who claim that milk secretion may be initiated in virgin girls who have attempted to quiet an infant by offering it the breast.

Testis

We have confirmed the observations of previous investigators concerning testicular atrophy which follows removal of the hypophysis in

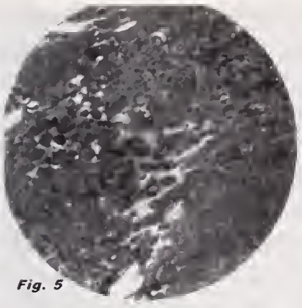


Fig. 5

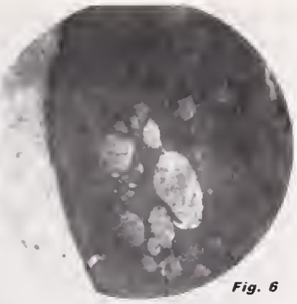


Fig. 6

Fig. 5. Placentoma in the uterus of a pseudopregnant mouse.

Fig. 6. Cysts in the adrenal cortex of a pseudopregnant mouse.

experimental animals. We also found, in confirmation of Philip E. Smith, that this atrophy can be prevented by the daily administration of hypophyseal implants. Our results differ, however, from those of Smith, insofar as the effect of A.P.L. is concerned. Administration of even large doses of A.P.L. has consistently failed to stimulate sperm cell formation in hypophysectomized rats. The interstitial tissue hypertrophy which follows A.P.L. administration in the normal animal is not influenced by the removal of the gland, but–just as in the normal–this hormone has no effect on the seminal epithelium after hypophysectomy (7).

In this connection it is interesting to note that the very immature male rat seems to react in the same manner to A.P.L. as does the older animal, the only clean-cut effect being proliferation of the interstitial tissue. Unlike the ovary, the testis reacts in the same manner after A.P.L. administration in the immature or hypophysectomized rat as it does in the mature male.

THYROID

That there is a very close relationship between the anterior pituitary and the thyroid glands has been very clearly established both experimentally and clinically. Cushing (1912) (40) observed in the dog that, following a transient hyperplasia occurring about 24 hours after hypophysectomy, involution of the gland ultimately resulted. Allen reported that the thyroid of tadpoles became atrophic following removal of the pituitary, and he noted that the implantation of the pituitaries of frogs caused a restoration of the thyroid to normal (41). P. E. Smith obtained similar results in the case of the white rat (43).

Clinical evidence pointing to the control of the thyroid by the pituitary has been abundantly available. Graubner (44), in a review of 34 cases of hypophyseal cachexia (Simmonds' disease) reported in the literature, found that in all cases the thyroid was reported as being small and atrophic and sometimes even sclerotic. As a result of the considerable experience which we have had in our own laboratory with hypophysectomized animals, we can confirm these findings in regard to the atrophic changes in the thyroid of dogs, monkeys, guinea-pigs, mice and rats from which the hypophysis has been removed.

Hyperplasia of the thyroid gland has been produced in a number of different species of animals by injections of anterior pituitary extracts. This fact completes the chain of evidence proving that the anterior pituitary normally exercises a controlling influence over the thyroid by means of an internal secretion.

Animals in which the thyroid stimulating action of the anterior pituitary has been conclusively demonstrated are the guinea-pig (Loeb and Bassett, 1929, 45; Aron, 1930, 46, 47; Janssen and Loeser, 1931, 48; Krogh, 1932, 49; Grab, 1932, 50), the cat (Schittenhelm and Eisler, 1932, 51), the dog (Houssay, 1932, 52), the rabbit (Baumann and Marine, 1932, 53), the pigeon (Riddle and Polhemus, 1931, 54), the duck (Schockaert, 1932, 55), and the rat (Anderson, 56, and Anderson and Collip, 1933, 9). Some of these workers reported failure to produce hyperplasia in the thyroid of the rat. It is of particular interest therefore to note that Dr. Evelyn Anderson, working with us, *was able to produce marked thyroid hyperplasia with hyperthyroidism, in the rat treated with crude pituitary extract plus Staphylococcus aureus vaccine.* Junkmann and Schoeller have found that the pituitary of the rat is relatively very rich in the thyreotropic substance compared with the pituitary of the guinea-pig, as determined by implantation into test guinea-pigs, and that the rat is much less sensitive than the guinea-pig to the thyreotropic hormone. In this connection, I should venture to suggest that it *may follow as a general rule that the sensitivity or responsiveness of an animal to injected hormone varies inversely with the hormone content or production of the animal's own gland.*

Hyperplasia of the thyroid of the rat has been produced by other means than the injection of highly potent thyreotropic hormone. Thus McCarrison has observed thyroid enlargement and hyperplasia in rats to which have been fed cultures of bacteria from the faeces of goitrous persons. We have seen extreme hyperplasia without hyperthyroidism in certain rats obtained from a dealer and kindly supplied to us by Dr. C. N. H. Long of Philadelphia, who had noted the condition and was

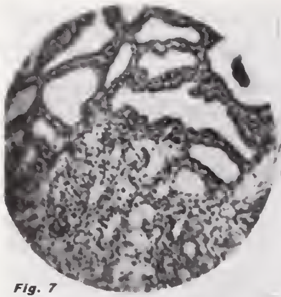


Fig. 7

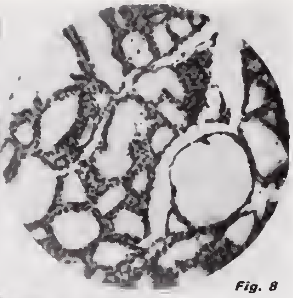


Fig. 8

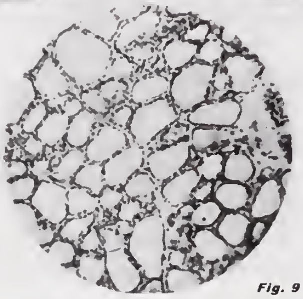


Fig. 9

Fig. 7. Control thyroid of goitrous rat. Weight 143 mg., metabolic rate 86 per cent of normal.

Fig. 8. Thyroid of goitrous rat after 9 days treatment with thyreotropic hormones. Note large vesicle, with flattened epithelium, filled with dense colloid. Weight 138 mg., metabolic rate 230 per cent of normal.

Fig. 9. Thyroid of normal rat after 74 days treatment with thyreotropic hormone. Note similar appearance to that seen in untreated hypophysectomized rat.

so kind as to send them on to us for use in our work.

The use of a non-specific agent such as a killed culture of *Staphylococcus aureus* in conjunction with anterior pituitary extracts in order to produce thyroid hyperplasia and hyperthyroidism became quite unnecessary after we had succeeded in preparing the thyreotropic principle in concentrated and purified form.

Preparation of the thyreotropic hormone

The presence of the thyreotropic principle can be demonstrated in almost any type of simple extract of anterior pituitary glands. A variety of methods are therefore available for the preparation of extracts rich in this hormone. Loeser (58) described a method for preparing an active extract in the form of a dry powder. His process consisted of aqueous ammoniacal extraction of the acetone treated glands followed by removal of proteins with trichloracetic acid and precipitation of the active substance by acetone from the trichloracetic filtrate. Alcohol and acetone were subsequently used as precipitation reagents. Junkmann and Schoeller (59) have reported on the chemical properties of the thyreotropic extract.

The method which we use to prepare an active extract is as follows: The combined filtrates obtained at the $Ca_3(PO_4)_2$ adsorption stage in the Q process for growth principle are concentrated and saturated with $(NH_4)_2SO_4$. The precipitate is taken up in distilled water and again precipitated with $(NH_4)_2SO_4$. Alcohol is added to the neutral aqueous extract of the precipitate to make 70 per cent by volume of this reagent in the mixture. The precipitate is collected on a filter and extracted with distilled water. An equal volume of acetone is added and the precipitate is collected on a filter and extracted with distilled water. This solution represents the final product, but further purification for the purpose of reducing the content of contaminating adrenotropic principle can be accomplished by repeated precipitation from 50 per cent acetone.

Most excellent preparations of the thyreotropic plus some adrenotropic hormone can be prepared by working up the combined filtrates from the above process by concentration and precipitation from 90 per cent alcohol.

The physiology of the thyreotropic hormone

The administration of adequate amounts of the thyreotropic hormone to normal animals results in the course of a few days in enlargement and hyperplasia of the thyroid. There is an increase in the metabolic rate (Siebort and Smith, 57, Verzar and Wahl, 61), increased heart rate (Schittenhelm and Eisler, 51), exophthalmos (Schockaert, 55, Loeb and Friedmann, 61), a reduction of the iodine content of the gland (Loeser, 58; Schockaert and Foster, 62), an increase in the alcohol-insoluble iodine of the blood (Closs, Loeb and MacKay, 63; Grab, 64; Schittenhelm and Eisler, 51), a depletion of liver glycogen and an increase in the acetone bodies in the blood Eitel and Loeser, 65; (Eitel, Löhr and Loeser, 66). Verzar and others have shown that none of the signs of hyperthyroidism can be produced in thyroidectomized animals by injections of thyreotropic hormone extracts (60).

Since the guinea-pig is exceedingly sensitive to the thyreotropic hormone, we made use of this animal as a test object in our earlier work on the purification of extracts.

The metabolic effect of bi-daily injections of an active extract into a group of 16 prepubertal guinea-pigs consisted of an average increase of 129 per cent on the 4th day and 134 per cent by the 6th to 8th day. The animals were killed after one week of injections, and the thyroid glands were more than doubled in size as compared with the controls; and the histological picture was that of extreme hyperplasia. Our Q extract and A.P.L. tested in a similar manner gave negative results.

From a study of the changes in metabolism from day to day in guinea-pigs and rats injected with the thyreotropic hormone, it is evident that there is a preliminary rise sometime within the first four days. This is followed by a secondary rise in about a week. This latter rise is not maintained, and a decline to normal or even subnormal levels gradually takes place. Since it has been shown by a number of workers that, following the injection of the thyreotropic hormone, there occurs an outpouring of thyroid secretion, one might suggest that the first rise in metabolism is due to the sudden discharge of existing stores of thyroid hormone into the blood stream, while the second rise follows after the hyperplasia of the gland, induced by the hormone, has advanced sufficiently to give an increased production of the thyroid hormone. The subsequent decline in metabolic rate has been made a subject of special study in our laboratory, but I shall defer until a little later a full discussion of our results.

The average increase in metabolic rate which we have seen in normal rats of our colony, treated with the thyreotropic hormone, has been +35 per cent. The administration of even massive doses of the hormone does not result in higher values. We obtained quite different results, however, with a small series of goitrous rats to which reference has already been made. A control animal in this group had a thyroid gland weighing 142 mg as compared with a normal rat's gland of 20 mg. The gland proved, on microscopic examination, to be extremely hyperplastic. The control metabolic rates of these animals was slightly subnormal. Immediately following treatment with thyreotropic hormone the metabolic rate rose rapidly. One animal showed a 95 per cent increase within 24 hours. The highest rate observed in the group was 262 per cent above normal. This was on the ninth day of injections. All of the rats showed definite symptoms of hyperthyroidism, irritability, weakness, exophthalmos and excessive sweating, and there was a 20 per cent loss of weight in the course of nine days.

Hypophysectomized rats show a decline in the metabolic rate to an average of 74 per cent of normal as determined on a series of 118 of our experimental animals. The thyroid gland decreases in weight and the microscopic picture is one of marked involution of the cellular elements. We have found that these animals are much more sensitive to injections of the thyreotropic hormone than are normal animals. They compare very favorably in this respect with the guinea-pig. The metabolic rate has frequently been restored to normal within a week with bi-daily doses of as little as 0.005 cc. of a purified thyreotropic extract. The normal rat has required at least 0.08 cc. bi-daily to give a similar response. We have chosen as an arbitrary unit of the thyreotropic hormone the minimum amount, administered daily in two injections, which will cause a rise of 20 per cent in the metabolism of the hypophysectomized rat by the fourth day. We believe that this unit compares fairly well with the Junkmann-Schoeller unit as determined by the use of the normal guinea-pig, but it has this advantage that the metabolism of the hypophysectomized animal, both before and during treatment, is far less variable than the histological picture of the guinea-pig's thyroid. The normal guinea-pig thyroid is extremely sensitive to the thyreotropic hormone stimulus, but unfortunately control animals all too frequently, in our experience, have shown mild thyroid hyperplasia.

We have no evidence of our purified thyreotropic extract causing growth in hypophysectomized animals that have been treated for some weeks. Thus, 40 hypophysectomized rats had an average weight of 121 gm before injections of the thyreotropic extract were commenced, and an average weight of 110 gm after 3–4 weeks.

Effects of the thyreotropic hormone on metabolism

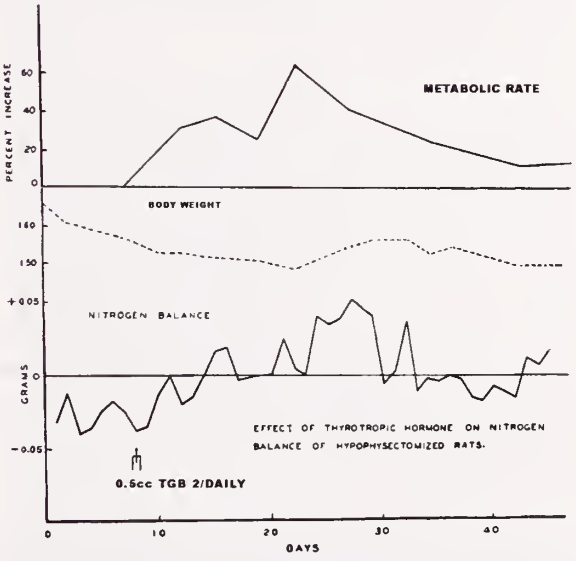


Chart 8. Effect of the thyreotropic principle upon nitrogen balance in hypophysectomized animals (Mr. Peter Black).

It is well known that thyroid feeding causes a creatinuria (Cramer and Krause, 1913). Dr. David Barr observed an increased creatine excretion in a

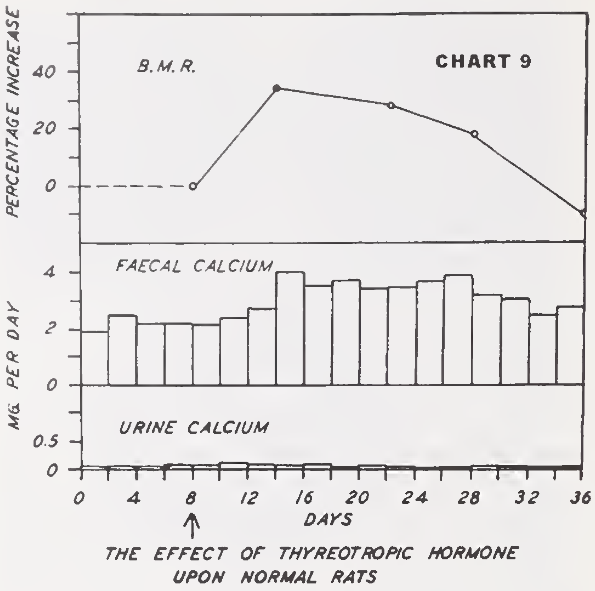


Chart 9. Effect of the thyreoropic extract upon calcium excretion (Dr.Leonard Pugsley).

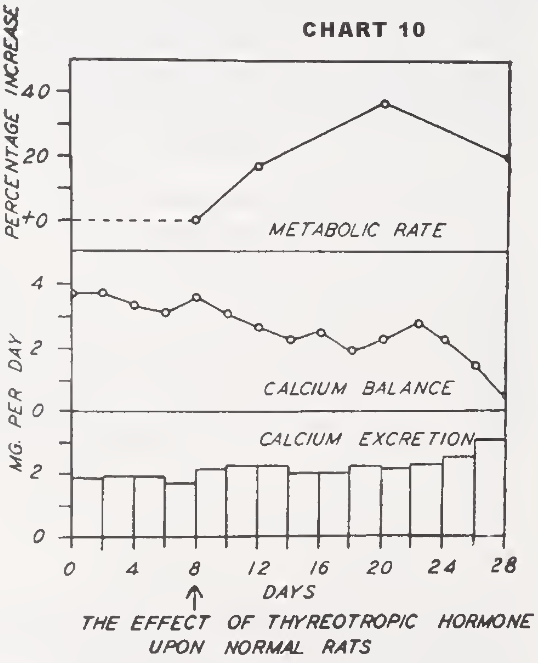


Chart 10. Effect of the thyreotropic hormone upon the calcium balance of normal rats (Dr. Leonard Pugsley).

patient given our T.G. extract. It is of interest, therefore, to compare the effects of thyroid feeding and of thyreotropic hormone injections upon the creatine excretion in relation to the changes produced by each in metabolic level. This part of the work has been carried out by Dr. L. Pugsley and Dr. Evelyn Anderson. The feeding of desiccated thyroid to normal rats caused a rise in the creatine excretion which reached a peak on the 10th day. The creatine excretion then gradually decreased, while the metabolic rate was still rising. The thyreotropic hormone caused a temporary increase in creatine excretion, both in normal and hypophysectomized rats. As in the case of the metabolic rate response, the former were less sensitive than the latter. Six units caused a definite increase in excretion in the normal rats, and one unit acted similarly in the hypophysectomized animals. An increased creatine excretion was likewise noted in the dog treated with the thyreotopic extract. Purified extracts of the growth and adrenotropic hormones had no effect on the creatine excretion of normal rats.

We see here two definite examples of the principle which I enunciated above; namely, *that the responsiveness of an animal to an administered glandular extract may vary inversely with the hormone content or production of the animal's own gland.* The principle may be illustrated by a specific example. The pituitary of the rat is relatively rich in the thyreotropic substance; the thyroid gland of the normal rat is relatively very active and the metabolic rate is accordingly relatively high. The normal rat is relatively insensitive to thyreotropic hormone. The hypophysectomized animal cannot produce thyreotropic hormone; the thyroid gland of the animal is relatively inactive and the metabolic rate is depressed, *but the sensitivity to injected thyreotropic hormone is at least ten times greater than in the case of the normal rat.*

Mr. Peter Black has extended the study of the effects of thyreotropic hormone extracts to fish. Here the effects are in general as they are in the mammal. The interesting observation was made, however, that untreated fresh fish placed in the water in which injected fish had previously been kept likewise showed an increase in the metabolic rate. The addition of the hormone to the water in which untreated fish were kept had no effect. It appears, therefore, that, in the case of the fish (cat-fish) the injection of thyreotropic hormone causes the liberation into the water of a substance which can be taken up by another fish with a resultant increase in metabolism of the latter animal. Further investigation along these lines will be carried out to determine if possible whether it is the true secretion of the thyroid which is passed into the water from the thyroid gland of the injected fish.

One of the effects of thyroid feeding is an increase in the calcium excretion by the bowel (91). Doctor Pugsley has been able to demonstrate a similar, though not so marked, effect in normal animals injected with the thyreotropic hormone which occurred only during a period of elevated metabolic rate.

A remarkable demonstration of the fact that the thyreotropic hormone has a direct action upon the thyroid cells has been given by Eitel, Krebs and Loeser, who produced hyperplasia in sliced thyroid tissue treated in vitro with an active thyreotropic extract. Houssay, Biasotti and Magdalena, and Marine and Rosen (92) have likewise obtained a reaction in transplanted thyroids.

ADRENAL

While the earlier workers, like Aschner, found no adrenal cortical atrophy in hypophysectomized dogs, more recent observations (Smith and others) have shown that definite atrophy of the adrenal cortex follows the removal of the hypophysis in rats. We were able to confirm these observations on the rat, and furthermore found that similar atrophy of the adrenal cortex may be produced in mice, guinea-pigs and monkeys. It is remarkable that the cortical atrophy which is so obvious after removal of the hypophysis in rats, mice and cats is not very marked in the hypophysectomized dogs so far examined by us. In the case of a dog hypophysectomized one month before autopsy, the width of the adrenal cortex was not markedly less than that of the normal control litter mate.

Histologically this cortical atrophy is characterized first by an intense hyperaemia of the cortico-medullary junction; then the zona fasciculata and zona reticularis of the cortex show definite signs of atrophy (fig. 10). The cells degenerate, and the cortex becomes progressively narrower. Numerous pigment cells appear in the zona reticularis, which contain yellowish green granules. Such cells may also appear in this zone in the normal rat during old age, but they are never found in young animals, and even in the senile rat they are never as frequent as they are after hypophysectomy.

Fig 10

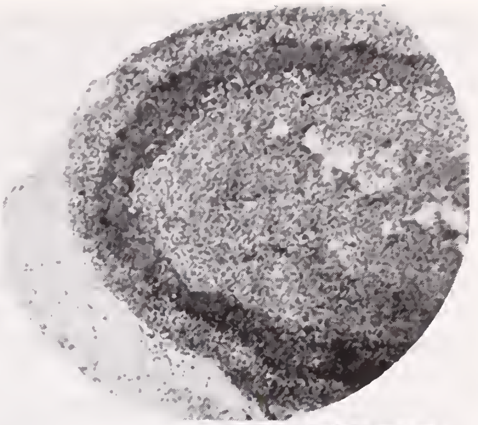


Fig. 11

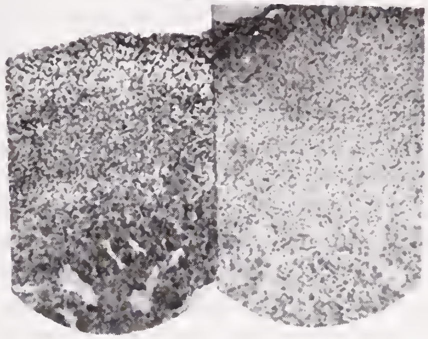


Fig. 10. Cortical atrophy in rat 265 days after hypophysectomy.

Fig. 11. Cortical repair with adrenotropic hormone 139 days after hypophysectomy. Left–control biopsy weight 3.5 mg. Right – 6 days after treatment weight 7 mg.

Preparation of the adrenotropic hormone

The alcohol and acetone filtrates which are obtained in the preparation of the thyreotropic principle are combined and concentrated at low temperature and pressure. The aqueous concentrate is saturated with ammonium sulphate and the precipitate is removed. It is extracted with 1 per cent aqueous ammonia and the extract is dialyzed, to remove the $(NH_4)_2SO_4$. After dialysis the extract is treated with ten volumes of absolute alcohol and the precipitate is removed and extracted with dilute aqueous alkali (0.05 NaOH). This extract is neutralized to pH 6 with dilute acetic and allowed to stand at 1°C for some days. The precipitate which has formed is removed and dissolved in either dilute acid pH 3 or dilute alkali pH 9. This isoelectric fraction which is obtained in the above manner is almost free of thyreotropic hormone and can be shown to be rich in adrenotropic principle by the following method of assay devised by Dr. Evelyn Anderson.

The left adrenal is removed from hypophysectomized rats ten days to two weeks following the operation. This gland is weighed and sectioned for microscopic examination. The animal is injected twice daily for six days with the extract to be tested. The animal is killed and the right adrenal is weighed and sectioned, as is also the thyroid gland. Control experiments have shown that there is no compensatory hypertrophy of the remaining gland after unilateral adrenalectomy in the hypophysectomized animal. Increase in weight of the remaining adrenal over that of the one taken at biopsy, together with microscopic evidence of cortical repair is taken as positive evidence of adrenotropic activity in the extract. The presence or absence of thyreotropic hormone can be determined in the same test animals by noting whether there is any increase in metabolism during the period of injections and if there is any evidence of increased cellular activity in the thyroid, taken at the post-mortem examination. It has been only in isoelectric fractions that we have obtained negative tests for thyreotropic hormone.

The purified adrenotropic hormone extract has been shown to withstand prolonged boiling at pH 5.

Physiological effects of the adrenotropic hormone

As yet we have very little detailed information on the physiological effects of the adrenotropic hormone. No appreciable improvement has been seen in the cachectic condition of the hypophysectomized rat treated with the active extract, even though a substantial degree of repair of the atrophic cortex has taken place (fig. 11). Normal animals injected with the extract have not shown any marked changes in the size or histological appearance of the adrenals. Dr. Pugsley has obtained, in a preliminary study of the effect of the adrenotropic extract upon the calcium and potassium balance of normal rats, very suggestive evidence that, during the first four days of the administration of the hormone, the potassium balance tends to become less positive, whereas no effect was noted on the calcium balance.

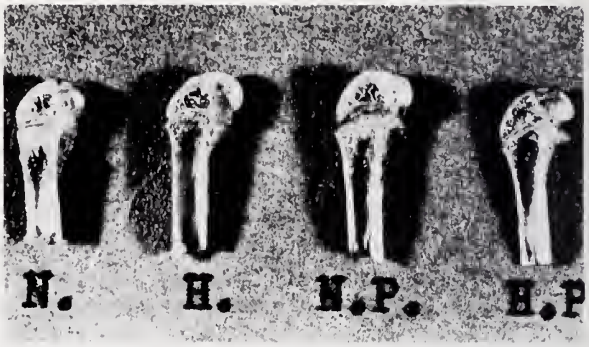


Fig. 12. Action of parathyroid hormone on bone of normal as compared with hypophysectomized rat. N-Normal. H-Hypophysectomized. N.P.-Normal treated. H.P.-Hypophysectomized treated.

PARATHYROID GLANDS

Hypophysectomy has produced no detectable changes in the parathyroid glands of the rats in our series. We can confirm Houssay that the parathyroids of the hypophysectomized depancreatized dog become atrophic. We have seen in one case a large focus of necrosis at the centre of one parathyroid, while the other showed definite signs of atrophy (fig. 13). We have seen definite enlargement of the parathyroids of the cat within two weeks of hypophysectomy. It is possible that there may be an early stage of parathyroid enlargement and over-activity which is later followed by atrophic change. Blood serum calcium of the hypophysectomized rat is normal or slightly increased. The calcium balance tends to be negative, but it has been restored to a definite positive value by treatment with the growth hormone (Pugsley) (67).

Hypophysectomized rats treated with the parathyroid hormone respond to it in the same manner as normal animals (Pugsley) (68) insofar as the early hypercalcuria is concerned (chart 11).

The effect of parathyroid hormone on the bone is quite different when applied in very large doses in acute experiments and in chronic experiments. While this hormone leads to bone resorp-

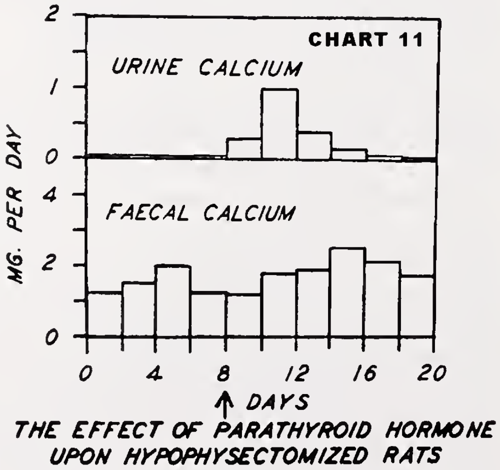


Chart 11. Showing that parathyroid hormone produces a hypercalcuria in the hypophysectomized rat (Dr. Leonard Pugsley).

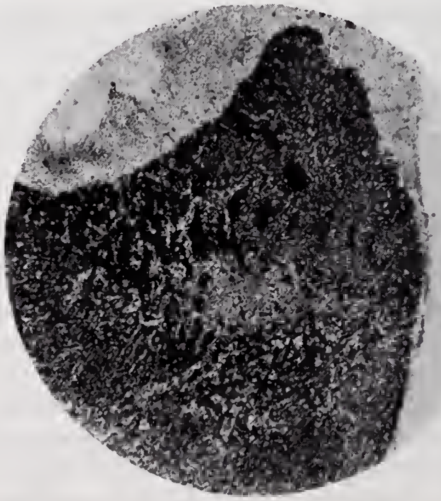


Fig. 13. Necrosis in the parathyroid of a pancreatectomized hypophysectomized dog, 10 weeks after hypophysectomy.

tion and formation of many osteoclasts in the acute experiment, the same substance leads to the formation of osteoblasts and to bone apposition when administered daily over long periods. We found that the same dose of parathyroid hormone which would lead to bone apposition and osteoblast formation in the normal animal leads to bone resorption in the hypophysectomized one. It seems, therefore, that the formation of new bone tissue is interfered with in the absence of the hypophysis (fig. 12).

THYMUS

The literature on the effect of hypophysectomy on the thymus is somewhat contradictory. P. E. Smith (1930, 69) saw no specific changes in the thymus of the hypophysectomized rat. Richter and Wislocki (1930, 70) noted enlargement of the thymus and lymph glands of the rat. Koster (1930) (71) found the thymus enlarged in the hypophysectomized dog. Sakamoto and Saito (1932, 72) described a condition of fatty degeneration in the thymus of hypophysectomised rabbits. Kapran (1932, 73) observed involution of the thymus of the dog after hypophysectomy. Our observations on the thymus of the hypophysectomized rat are in agreement with P. E. Smith's. We have frequently seen enlargement of the thymus in rats treated with certain extracts of anterior lobe for some weeks. The new tissue which could be separated from the old on account of the slightly lighter color of the new lobes proved on examination to be lymphatic in type. This effect has been noted in chronic experiments in which extracts rich in the adrenotropic hormone have been used. The significance of this is not yet understood, but it may be stated that there is suggestive evidence that certain of the blood-forming organs may be influenced by anterior pituitary principles. Miss Margaret Hill is studying this phase of the problem.

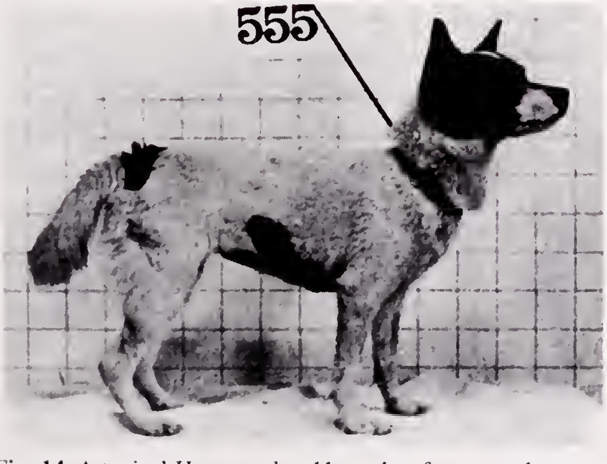


Fig. 14. A typical Houssay dog 11 weeks after second operation

The diabetogenic and ketogenic effects of anterior pituitary extracts

Burn and Ling (1930) (74) demonstrated that rats on a salt butter diet, injected with an alkaline extract of anterior lobes, excreted large amounts of acetone bodies in the urine. Hoffmann and Anselmino (1931) found that certain anterior lobe extracts caused an increase in the acetone bodies of the blood and also lowered the basal metabolism (75, 76). Funk (1932, 77) confirmed Hoffmann and Anselmino and stated that the fat hormone could be obtained from both normal and pregnancy urine. Magistris (1932, 78, 79) found an increase in the acetone bodies of the blood of rabbits treated with an aqueous extract of acetone dried powder pituitary preparation. He reported also a lowering of the metabolic rate. He was of the opinion that the fat metabolism hormone was not identical with the thyreotropic, growth or maturity factors.

Rietti (1932, 80) noted a decreased acetone excretion following either pancreatectomy or phloridzin administration to hypophysectomized as compared with normal dogs.

Evans (1933) reported that he had produced glycosuria in a female dog and obesity in a male animal by injections with his preparation of the growth hormone.

Houssay, et al. (1933, 82) reported that anterior lobe extracts inhibited the hypoglycaemia of hypophysectomized animals and increased the glycosuria, diuresis, and acetone body excretion

Fig. 15. Two hypophysectomized monkeys 10 weeks after operation

of hypophysectomized depancreatized animals. Barnes has reported somewhat similar results.

It is impossible to know from the earlier work whether the so-called diabetogenic principle and the so-called ketogenic principle are one and the same. It is possible that in each case we are dealing with a special physiological effect of one of the known pituitary hormones. The lowering of metabolism that has been observed by Hoffmann and Anselmino and by Magistris may have been due to the secondary effect of the thyreotropic principle. Using the Burn–Ling test object as a method of assay, Mr. Peter Black has been studying the ketogenic action of the various extracts of anterior lobe with which we have been working. This work has not yet advanced to the stage where final conclusions can be drawn, but the results so far obtained would tend to support the view of Magistris that the ketogenic substance is distinct from the thyreotropic substance.

The diabetogenic substance can be studied to best advantage in the Houssay dog, i.e., in the depancreatized and hypophysectomized animal. Dr. Barnes very kindly tested some of our extracts on his Houssay animal last year. Diabetogenic activity was found by him in both the growth and the thyreotropic fractions. We are at present in our own laboratory attempting to build up a colony of Houssay dogs together with a number of hypophysectomized animals of different species. We have been able to confirm Houssay, Barnes and others in regard to the effect of hypophysectomy upon the diabetic condition of totally depancreatized animals.

We have lost some of our completely hypophysectomized monkeys from hypoglycaemia and one Houssay dog died presumably from hypoglycaemia. This particular animal was an exception to the general rule as regards the blood sugar. Fasting values of 50 mg had been observed previous to death. The treatment with extracts to which this animal had been subjected no doubt contributed in part to the unusual blood sugar values which had been observed over a period of many days. These points will be discussed in detail later. I would like to mention here that we have lost four of our hypophysectomized cats approximately ten days after hypophysectomy all of which showed histological signs of liver degeneration.

ANTI-HORMONES

It has been a matter of great interest to those working in endocrinology to note in the case of many laboratory animals and also in the case of many patients, that a state of lowered reactivity, of increased resistance or of actual non-responsiveness may gradually become manifested in those that have been treated for a long period with some glandular extract. Likewise, it has been observed that certain previously untreated animals or patients may be non-responsive to injections of a known potent glandular extract. We have only to think of the failure of the parathyroid hormone to affect appreciably the blood serum calcium of the rabbit or of the patient who is resistant to enormous doses of thyroid extract.

It was therefore a matter of more than usual interest to us when we found in chronic experiments on animals in which the thyreotropic hormone was injected twice daily over a long period that the animals not only failed absolutely to give a positive metabolic response, but actually showed a lowering of the metabolism to the level of that of hypophysectomized animals (83). The thyroid glands of the chronically injected animals became atrophic and the thyreotropic hormone was absent from their own pituitary glands (fig. 16). In my Washington lecture to the Congress of Physicians and Surgeons published last September, I asked the following questions anent this remarkable fact:

> "Does the thyroid gland develop an immunity to the injected hormone?
>
> Is some inhibitory mechanism brought into action by the continued stimulation with the thyreotropic hormone?
>
> Does the purified extract used contain as well a true inhibitory principle which has a definite latent period before its effects become manifested?"

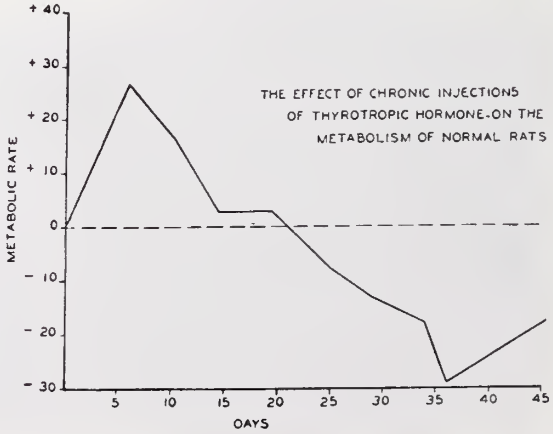


Chart 12. The average metabolic rate curve of a group of normal rats injected daily with the thyreotropic hormone. Note the fall to subnormal levels after 30 days treatment.

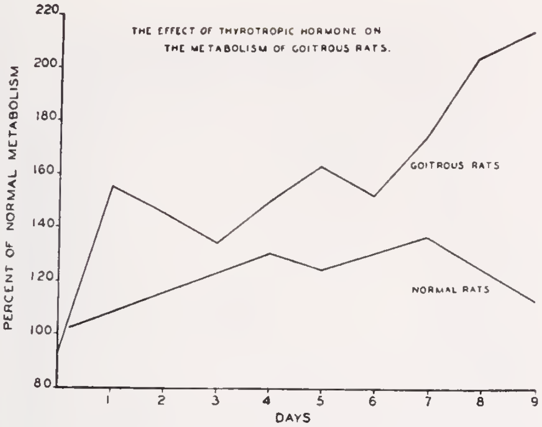


Chart 13. A comparison of the metabolic response in normal and goitrous rats treated with the thyreotropic hormone.

In the light of our recent experiments, our second question would appear to be the most pertinent. Dr. Evelyn Anderson and I have been able to demonstrate most positively that the blood serum of the thyreotropic hormone resistant rats contains a substance, which we propose to call the antithyreotropic hormone, which when injected into normal rats confers upon them, for a time, resistance to the elevating effect of the thyreotropic hormone on the metabolic rate. Furthermore, we have extended our studies to other species, and we have produced the antithyreotropic hormone substance in the blood of the rabbit, goat, dog and horse, by daily injections of adequate amounts of the thyreotropic hormone extract. Dr. Carl Bachman has obtained negative results with the active serum using the complement fixation and precipitin tests. This encouraged us to prepare serum-protein-free extracts of the antithyreotropic blood. This proved to be entirely feasible and now concentrated and highly active antithyreotropic hormone extracts are a fact (83).

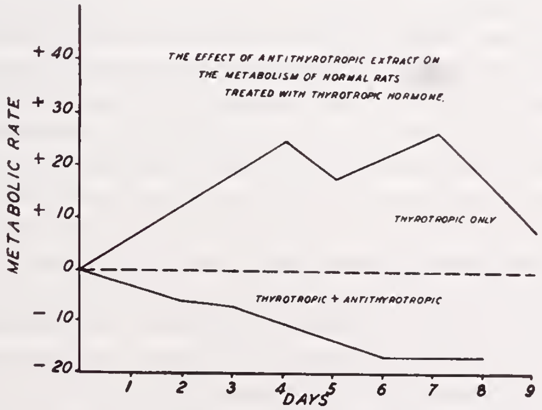


Chart 14. The demonstration of the anti-thyreotropic effect of the purified extract of horse serum from an animal injected with the thyreotropic hormone.

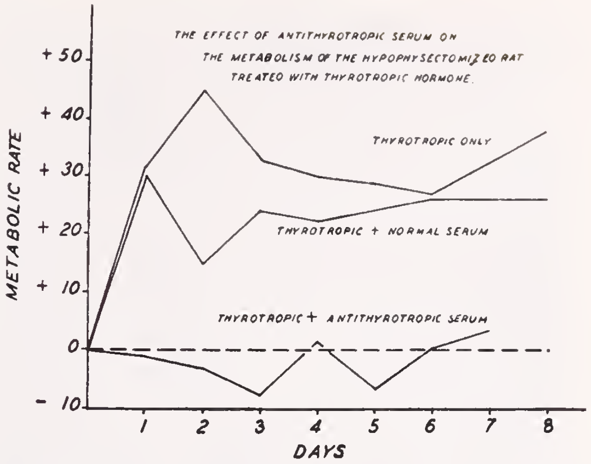


Chart 15. The metabolic effect in hypophysectomized rats treated (1) with thyreotropic hormone; (2) thyreotropic hormone + normal serum; (3) thyreotropic hormone + antithyreotropic serum.

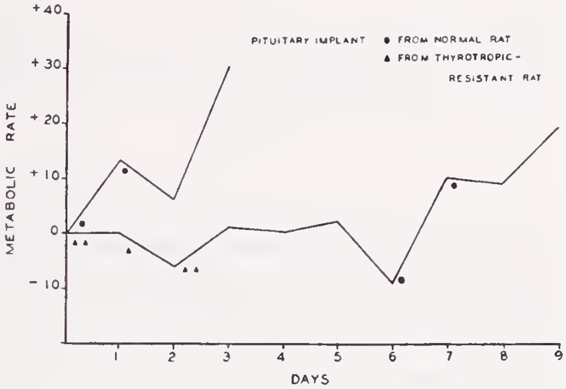


Chart 16. Showing absence of thyreotropic principle in the pituitary of the normal rat treated for some weeks with the thyreotropic extract. Upper curve (control) shows the effect of implantation of two normal pituitary glands and lower curve shows the non-effect of implantation of five pituitaries from chronic thyreotropic hormone treated rats. Later the implantation of two normal glands caused a sharp rise in the metabolie rate as shown on the lower curve.

We have adopted as a working hypothesis the view that antihormones are present in the normal subject. If this is true then the production of some of those antihormone substances which we have reported can be looked upon as an increasing of the level of a substance or substances which are normally present. This broad principle is particularly attractive, since it may be used to explain such things as the great difference in the responsiveness of different species to hormones, as well as minor variations in responsiveness within a species. The extreme case is illustrated by the hypophysectomized animal, which shows not only a lack of thyreotropic hormone, since the seat of its production has been destroyed, but a decrease in the antithyreotropic substance, which is shown indirectly by the increased

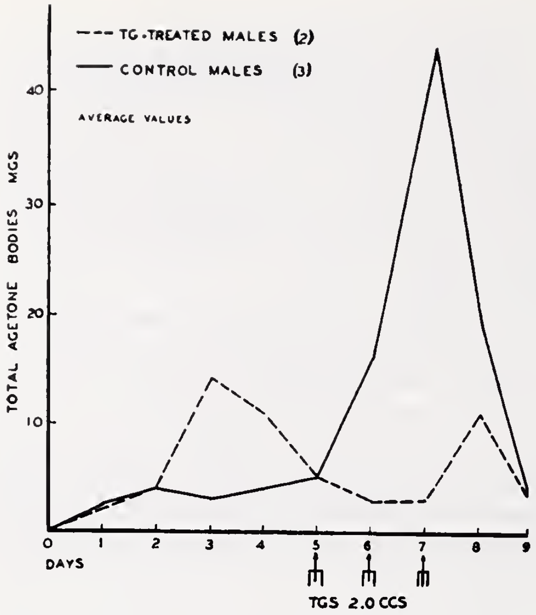


Chart 17. Showing the ketogenic effect of thyreotropic extract T.G. in normal rats and the non-effect of similar treatment in normal animals treated for some weeks with the thyreotropic extract (Mr. Peter Black).

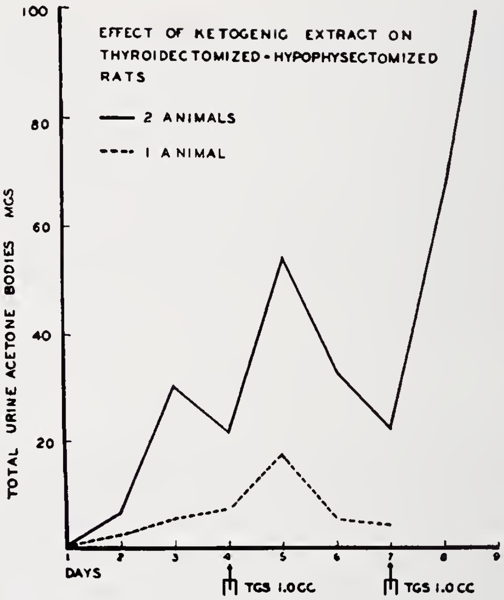


Chart 18. Showing that the ketogenic effect can be obtained in an otherwise untreated hypophysectomized-thyroidectomized animal by the administration of an anterior pituitary extract, T.G. (Mr. Peter Black).

sensitivity to the thyreotropic extract. It is possible, in view of this, that many apparent hypoglandular states may be due to an increase in antihormone level.

The detection of an antihormone in the blood is already possible in the case of the antithyreotropic substance.

One of the most important implications of this theory of "inverse response" is that the level of a hormone is related directly to the level of the corresponding antihormone. The demonstration of a hyperhormone state, associated with lowered responsiveness to injected hormone, implies the co-existence of a hyper-antihormone state. One might here draw an analogy between the highly buffered solution which is sluggish in regard to pH change on addition of small amounts of acid or alkali, and the hormone resistant animal which is, as it were, well buffered by a high level of hormone and antihormone substances in its system.

That the effect of a small dose of a hormone will be greater when the existing concentrations of hormone and antihormone circulating are small than when they are already large, will not be regarded as surprising. In many cases of physiological antagonism between drugs, it is known that the ratio between the concentrations of the two antagonists determines the physiological effect, whatever the actual amounts; this has been shown for the interaction of atropine and pilocarpine on salivary secretion (86), of atropine and acetylcholine on the frog ventricle (84, 87), of adrenaline and ergotamine on the rabbit uterus (88) and elsewhere. The *ratio* will obviously be more disturbed by a given amount of hormone when the quantities of hormone and antihormone present are initially small.

The facts which have been proven with regard to the thyreotropic hormone suggest that the principle of *inverse responsiveness* may apply very generally. If it can be shown that somewhat similar conditions hold in the case of other hormones, then a general law—that of *"inverse response"*—may exist. There is already existent considerable support for this as a general basic view.

We have found that the growth hormone has no effect upon the rate of growth of young male rats and only a slight positive effect in the case of females (chart 1). Hypophysectomized animals, male or female, are exceedingly sensitive to the growth hormone. Immature female rodents are extremely sensitive to the various forms of oestrin. Thyroidectomized animals show an increased sensitivity to thyroid extract (93). Hypophysectomized animals are much more reactive to the diabetogenic substance than are normals. Other examples of apparent non-reactivity to hormones resulting from chronic treatment are to be found in the literature. Akimoto found that rabbits showed little or no increase in blood sugar after adrenalin administration provided they had been previously treated with adrenalin for 10-20

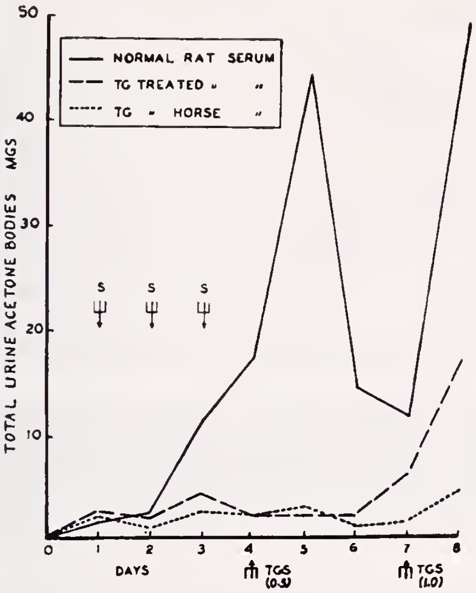


Chart 19. Showing anti-ketogenic effect of serum of the rat and horse treated with thyreotropic extract for some weeks as compared with the non-inhibitory effect of normal serum.

days. Zondek reported that mice treated with prolan first showed great increase in ovarian weight but that after a certain time the weight of the ovary was normal in spite of continued injections of prolan. Aron confirmed these observations in the guinea-pig, and further showed that the same loss of sensitivity developed after chronic treatment of the guinea-pig with pituitary gonadotropic extracts. Our own results on rats treated with A.P.L. or pituitary implants confirm these findings; and we were able to show also that the ovaries of such chronically treated animals not only return to normal weight but often to subnormal size and show definite histological evidence of severe atrophy.

de Fremery, Luchs and Tausk (85) made the observation that by continuous administration of corpus lutein hormone one is unable to maintain the uterine mucosa of the rabbit in a progestional. stage for more than approximately 17 days. After this the mucosa atrophies whether the hormone administration is continued or not. Hartman and Winter have observed recently that adrenalectomized animals treated with cortin over a long period may become non-responsive and show definite signs of cortical deficiency, although they are treated with large amounts of a potent cortical extract. Loeb and Friedman (1931) observed that guinea-pigs treated with thyreotropic anterior lobe extract lost their sensitivity after a period of 15 – 17 days. Aron (1932) obtained a similar result. In our own extensive experiments with the purified hormone on rats we have confirmed and extended these observations to the point where the nature of the mechanism underlying such reactions has become manifested.

We have been able to demonstrate that rats become non-responsive to the gonadotropic effect of the anterior pituitary-like hormone of the placenta and also to the maturity factor present in fresh rat pituitary by repeated daily treatment with these substances. It is of special significance that in the non-responsive state, the gonad may become smaller than in the normal and show definite signs of atrophy. Ovaries that have reached this state as a result of chronic A.P.L. treatment still respond to the gonadotropic substance in fresh pituitary implants. Similarly ovaries that have become resistant to the gonadotropic hormone of implants still respond to the placental hormone. Furthermore, the blood serum of rats injected for many weeks with A.P.L. has been shown to inhibit the ovary-stimulating effect of A.P.L. in the immature animal. Also the blood serum of an A.P.L. chronically injected rabbit has been shown to inhibit A.P.L. in the immature rat.

Hypophysectomized rats which have been treated for some weeks with our purified growth extract have ceased to grow and indeed have actually shown a decline in the growth curve even though the injections of known potent extract have been continued (chart 2). A group of such growth hormone resistant animals were sacrificed and the blood serum of these was pooled. A suggestive result was obtained when this serum was used in conjunction with a standard growth extract. The test object, a recently hypophysectomized rat, did not show as great a growth response as did the control treated with growth extract plus normal serum. Since, for complete inhibition of the growth hormone action, a very definite amount of antihormone must be required in relation to the growth hormone used, a new method of testing for the antigrowth principle was devised. This consists in the continuous injection twice daily of a standard dose of Q extract. Antiserum is given in addition as soon as a definite growth effect is manifested. A positive effect consists in a slowing or the complete inhibition of the growth effect of the Q extract. In the course of a few days, when this has become established, normal serum is substituted for the antigrowth serum. Growth is then resumed as in the first period. Antiserum is again introduced until growth ceases or is greatly slowed and again the positive effect is restored by normal serum used in place of the antigrowth serum being tested.

Our antigrowth serum has been prepared by injecting a horse daily with the Q extract.

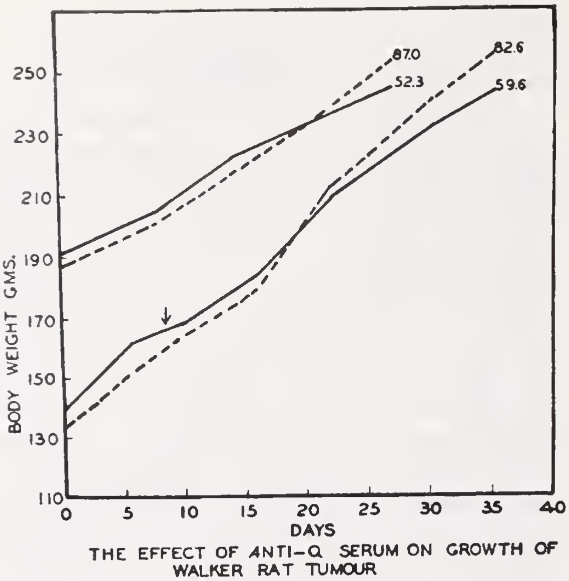


Chart 20. Growth curves of rats bearing the Walker tumour and treated with the anti-Q horse serum. Note that the average weight of the tumours in the case of the treated animals (broken line) was considerably less than in the controls (5 animals in each group) (Dr. C. S. McEuen).

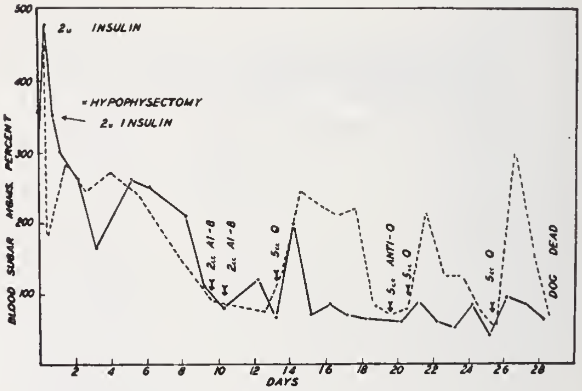


Chart 21. Dotted line–evening blood sugars. Solid line–morning blood sugars of a Houssay dog. Adrenotropic extract A.I., growth extract Q and anti-Q (horse serum) were administered. Shows suggestive evidence of a neutralizing of the diabetogenic effect of Q extract by the anti-Q horse serum.

Dr. C. S. McEuen has been studying the effects of various hormones on the Walker-rat tumour. Since the most positive type of inhibitory influence upon the growth of this tumour was shown to be manifested after hypophysectomy (McEuen and Thomson, 89) and since therefore there is evidence that the rapid growth of this tumour is related to a normal if not to a hyper- functioning anterior pituitary of the host, Dr. C. S. McEuen has carried out some preliminary experiments in which horse serum from the animal treated with Q extract has been injected into tumour bearing animals. The results of this preliminary test are highly suggestive (chart 20) and justify the further work along these lines which is being undertaken. The chief difficulty in the way of a practical application of the antigrowth principle is suggested by the failure of an antigrowth serum, which has been shown to be potent by the method outlined above, to affect appreciably the rate of growth of normal rats. This is due very probably to the great functional reserve which the normal pituitary must possess. Much more valuable information will be at hand when we have had an opportunity to complete a series of experiments in which the effects of continuous injections, for long periods, of antihormone principles of various types have been ascertained.

ANTI-DIABETOGENIC PRINCIPLE

As stated before, there is no positive evidence as yet as to whether the diabetogenic effect of anterior pituitary extracts is due to a specific principle or whether it is a side effect of one of the known pituitary hormones. Since our Q extract has been found to be diabetogenic, it was of interest to see if any anti-diabetogenic effect could be demonstrated in the serum of the horse chronically injected with Q extract. Due to the fact that normal animals are useless in this type of testing, we have confined our efforts to the Houssay dog. Here again there is great difficulty because the average Houssay animal has a blood sugar of 250 mg. and excretes large amounts of sugar. One animal which had been treated for some weeks with oestrogenic extracts of placenta and pregnancy urine prior to the Houssay operation of pancreatectomy and hypophysectomy did have a fasting blood sugar of less than 100 mg. This animal was treated with the Q extract and the antigrowth serum taken from hypophysectomized rats as indicated in the chart. The results are very suggestive of a neutralization of the diabetogenic action of the Q extract by the anti-Q serum. They are not conclusive, however, but they have encouraged us to extend the research along these same lines.

ANTI-KETOGENIC PRINCIPLE

Using what is no doubt altogether too artificial a test object, normal rats on a butter diet (Burn and Ling)–Mr. Peter Black has found that animals which have become non-responsive to the thyreotropic hormone do not give a positive result by the Burn-Ling test for acetone body excretion. Also he has decreased the ketogenic effect of the thyreotropic extract on normal animals by injecting them with antithyreotropic

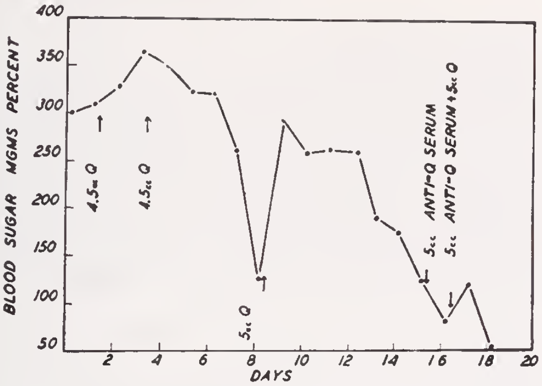


Chart 22. Houssay dog—morning blood sugars. Q extract, diabetogenic and anti-Q serum administered as shown on chart. Like no. 21, shows suggestive evidence of a neutralizing of the diabetogenic effect of Q extract by the anti-Q serum.

serum. These results, while not free of criticism, nevertheless suggest the interesting possibility that the diabetogenic effect (hyperglycaemia and glycosuria) and the ketogenic effect (increased excretion of acetone bodies; may be mediated through two entirely different mechanisms (charts 17, 18, 19).

THE ANTI-ADRENOTROPIC SUBSTANCE

We have as yet no experimental evidence to submit which would establish the existence of such a principle, although we confidently believe that such exists.

CLINICAL APPLICATIONS

Hormone therapy of any kind must be approached with much greater caution than has been the case in the past. While the results of our recent work suggest that many new dangers may attend the clinical use of glandular extracts, they also point the way to new applications. If the general principles established by the animal work are applicable to the human subject, then one must consider the possibility both of creating antihormones in an active way in the system of the patient, and of increasing the antihormone level by use of active extracts of the serum of horses or other animals which have been treated for long periods with the respective hormone.

I should like to point out, in bringing this discussion to a close, that some of the statements which I have made represent final conclusions which I trust will stand the test of time; some on the other hand are the expression of a point of view in keeping with the results of experiments made; and finally, some are purely speculative. The part of the work of which I have spoken that has been carried out in the Biochemistry Department of McGill University has been due to the splendid cooperation of a relatively large group of workers to whom all credit must be given for such positive findings as have been made.

The members of this team are Drs. E. M. Anderson, C. Bachman, R. L. Kutz, C. S. McEuen, 11. Mortimer, L. I. Pugsley, H. Selye and D. L. Thomson; Miss Margaret Hill; and Messrs. P. T. Black, O. Denstedt and T. McKeown.

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Abstracts

*The following abstracts were presented by investigators at the Sixteenth Annual Samuel Bronfman Department of Medicine Research Day at the Mount Sinai Medical Center. Most of the investigators serve in the Samuel Bronfman Department of Medicine, including those working at affiliated institutions such as The Bronx Veterans Affairs Medical Center, Bronx, NY; Elmhurst Hospital Center, Elmhurst, NY; Queens Hospital Center, Jamaica, NY; Englewood Hospital and Medical Center, Englewood, NJ; and St. Joseph's Hospital and Medical Center, Paterson, NJ. The work outlined in three abstracts identified with an * were presented in the morning plenary session. Several additional posters were shown on Research Day, but the abstracts have been published elsewhere. Abstracts from Queens Hospital Center were presented as posters on Research Day held at that institution.*

Research in Medicine 1999
Mount Sinai School of Medicine

Alcohol Research

Study on the Toxicity of β-Carotene and Acetaldehyde Combination in HepG2 Cells. R. Ni, M.A. Leo, J. Zhao, and C.S. Lieber. Alcohol Research Center, Section of Liver Disease and Nutrition, Bronx VA Medical Center, Bronx, NY; and Mount Sinai School of Medicine, New York, NY.

In rats and baboons, the hepatotoxicity of chronic ethanol consumption was shown to be exacerbated by β-carotene feeding, but the mechanism of this adverse effect is unknown. To study this, human hepatoma-derived HepG2 cells were incubated for 24 hrs with acetaldehyde (initial concentration of 179 μM, maintained through repeated additions) and/or β-carotene (1-1.5 μM). The latter was incorporated in phosphatidylcholine liposomes to yield hepatocyte concentrations equivalent to those measured by HPLC *in vivo* in human liver. Either acetaldehyde or β-carotene resulted in hepatotoxicity, documented by a release of lactic dehydrogenase from the cells into the media: (4.2 ± 0.4 and 3.9 ± 0.2 vs. 2.9 ± 0.2 in controls, % of total; $p < 0.01$ and < 0.05 respectively). Combination of the two resulted in an additive effect (5.0 ± 0.3; $p < 0.001$). The toxic effect of β-carotene was also documented by an alteration of mitochondrial function assessed by the tetrazolium dye MTT (45.1% ± 0.99 of controls; $p < 0.001$). In that respect, β-carotene was more toxic than acetaldehyde ($p < 0.001$).

Conclusion: β-carotene, in concentrations equivalent to those seen in human livers *in vivo*, is toxic to HepG2 cells *in vitro* and its effect is exacerbated by acetaldehyde, the toxic metabolite of ethanol. This model system now provides a tool to study the mechanism of this clinically relevant toxic interaction.

Polyenylphosphatidylcholine Attenuates the Oxidation of LDL Produced by Alcohol Feeding in Baboons. K.P. Navder, E. Baraona, M.A. Leo, and C.S. Lieber. Alcohol Research Center, Bronx VA Medical Center, Bronx, NY; and Mount Sinai School of Medicine, New York, NY.

Alcohol taken in moderation may prevent atherosclerosis, whereas heavy drinking has the opposite effect, in part by promoting oxidation of low-density lipoproteins (LDL), a pathogenetic factor in atherogenesis. We assessed here (1) whether similar alterations can be reproduced in baboons fed 50% of energy as ethanol (the average intake of alcoholics) and (2) whether such alterations are affected by supplementation with polyenylphosphatidylcholine (PPC), a mixture of polyunsaturated phosphatidylcholines, shown to prevent alcoholic fatty liver, fibrosis and cirrhosis. Ten animals were given the ethanol-containing diet and ten were pair-fed isocaloric control diets for 7 – 8 years. In half of the pairs, the diets were supplemented with 2.8 g of PPC/1000 kcal. Alcohol feeding increased LDL-lipoperoxides and made LDL-proteins more negatively charged, changes that were attenuated or prevented by PPC. The oxidizability of LDL was determined *in vitro* by the formation of conjugated dienes following oxidation with Cu^{++}. Alcohol shortened the lag time (which measures LDL antioxidant capacity); this effect was normalized by PPC supplementation. By contrast, PPC produced no significant changes in the controls. LDL oxidation with either Cu^{++} or 2,2'-azobis (2-amidinopropane) dihydrochloride was prevented by dilinoleoyl-phosphatidyl choline, a major PPC component. Thus PPC, by markedly attenuating the ethanol-induced increase in LDL oxidation, opposes one of the effects whereby atherosclerosis is being promoted.

Circulating Markers of Fibrosis Effects of Alcohol Intoxication. Y. Ponomarenko[1], M.A. Leo[1], W. Kroll[2], and C.S. Lieber[1]. [1]Section of Liver Disease and Nutrition, Alcohol Research and Treatment Center, Bronx VA Medical Center, Bronx, NY; and Mount Sinai School of Medicine, New York, NY; and [2]Bayer AG, Wuppertal, Germany.

In recent years, a number of circulating breakdown products of collagen or other components of the extracellular matrix (ECM) have been proposed as markers of hepatic fibrosis. In addition, matrix degrading metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) have been considered to be key determinants of ECM deposition. However, the published results lack consistency. Since many of the patients with fibrosis studied were alcoholics, the question was raised whether the presence of alcohol may have affected the results obtained and whether some of the variability reflects drinking at the time of blood sampling. Indeed, in a preliminary study, we had observed that serum values of laminin, the major noncollagenous glycoprotein of basement membranes, decrease with abstinence. Using sandwich-type assays or RIA technology with corresponding antibodies, we now completed this observation and extended it to 7 additional markers. A group of ten alcoholics were studied while intoxicated and during the following 2 weeks of abstinence, verified with repeated breath alcohol measurements. In addition to laminin, measurements were carried out of tenascin, a molecule expressed in proliferating ECMs; undulin, a glycoprotein associated with the surface of mature fibrillar collagen; TIMP-1; collagen VI, a molecule that forms filaments between large collagen fibrils; the N-terminal propeptide of procollagen type III (PIIINP), considered a marker of fibrogenesis; hyaluronic acid (HA), a ubiquitous glycosaminoglycan with high extraction by the liver sinusoidal endothelium; and MMP-2. Laminin was significantly reduced at 1 week (22%, $p = 0.013$) and at 2 weeks (30%, $p = 0.02$). Similarly, tenascin and undulin also significantly decreased ($p = 0.03$). By contrast, TIMP-1, collagen VI, PIIINP, HA and MMP-2 did not significantly change. The mode of action of alcohol on these tests is unknown, but regardless of the mechanism involved, the present results indicate that the presence of alcohol in the blood should be taken into account in assessing the significance of the proposed markers of fibrosis.

Summary: Of the 8 circulating markers of liver fibrosis studied, 3 (laminin, undulin and tenascin) appeared to decrease upon withdrawal from alcohol intoxication, whereas the 5 other tests (TIMP-1, collagen VI, PIIINP, HA and MMP-2) remained unaffected; these differences, if confirmed in a larger series, must be considered when using those measurements to assess fibrosis.

Polyenylphosphatidylcholine (PPC) Corrects Alcohol-Induced Oxidative Stress and Associated Depletion of Dilinoleoyl-phosphatidylcholine (DLPC). S. Aleynik, M.A. Leo, L.M. DeCarli, and C.S. Lieber. Alcohol Research Center, Section of Liver Disease and Nutrition, Bronx VA Medical Center, Bronx, NY; and Mount Sinai School of Medicine, New York, NY.

As we showed before in baboons, both hepatic alcohol-induced oxidative stress and associated depletion of DLPC can be attenuated by the administration of PPC. We now determined whether this is associated with corresponding systemic changes assessed in the plasma. Baboons (*Papio hamadryas*) were fed Lieber-DeCarli liquid diets containing 50% of energy as ethanol (equivalent to the average consumption of the alcoholic) or isocaloric carbohydrates, with or without 2.8 grams of PPC per 1000 kcal for a period up to 8.3 ± 0.5 years. Alcohol resulted in a three-fold decrease of circulating DLPC (determined by HPLC). We found the same trend for some other phosphatidylcholines, whereas total plasma phospholipids, tocopherol and reduced glutathione (GSH) were not changed. PPC administration increased circulating DLPC and some other phosphatidylcholines to levels above those in untreated animals ($p < 0.01$). Alcohol feeding also resulted in a 3.5-fold ($p < 0.001$) elevation of plasma 4-hydroxynonenal (4-HNE, measured by GC/MS), reflecting the alcohol-induced systemic oxidative stress. This increase was fully prevented by PPC. There was only a trend for corresponding changes in plasma malondialdehyde. In conclusion, the alcohol-induced oxidative stress and the associated depletion in DLPC, shown previously in the liver, is also found in the plasma and can be fully prevented by PPC administration.

Alcohol-Induced Apoptosis of Hepatocytes and Its Modulation by Polyenylphosphatidylcholine (PPC) in a Rat Model. L-J. Mi, K.M. Mak, and C.S. Lieber. Alcohol Research and Treatment Center, Bronx VA Medical Center, Bronx, NY; and Mount Sinai School of Medicine, New York, NY.

Alcohol consumption increases apoptosis of hepatocytes. The alcohol-induced apoptosis appears to be mediated by cytochrome P450 2E1, oxidative stress and cytokines. PPC, a soybean extract rich in polyunsaturated phosphatidylcholines, decreases alcohol-induced oxidative stress and fibrosis in baboons, modulates cytokine production and attenuates fatty liver in rats. To assess whether PPC attenuates the alcohol-induced apoptosis of hepatocytes, formalin-fixed and paraffin-embedded liver tissues from 28 male Sprague-Dawley rats were studied using TUNEL (terminal transferase dUTP nick end labeling) assay. These rats were divided into four groups and pair-fed for 21 days with Lieber-DeCarli liquid diets containing 36% of energy as alcohol or an isocaloric amount of carbohydrate with PPC (3 g/L) or equivalent amounts of linoleate as safflower oil and of choline. An additional dose of alcohol (3 g/kg) was given intragastrically 90 minutes before the livers were removed. Apoptotic hepatocytes were identified by positive TUNEL staining and/or nuclear chromatin condensation or margination. 20,000 to 60,000 hepatocytes in each rat were counted by light microscopy using an Image-Pro Plus program. In alcohol-fed rats, the percentage of apoptotic hepatocytes was about three times greater than in control rats (0.205 ± 0.047% vs. 0.077 ± 0.008%, $p < 0.01$, $n = 7$). PPC feeding decreased the alcohol-induced apoptosis by half (0.116 ± 0.034%, $p < 0.05$, $n = 7$). No difference in apoptosis between the control and PPC-fed rats was found. Apoptosis appeared to be distributed randomly in the liver lobules. The liver from rats fed alcohol (with or without PPC) exhibited varying degrees of fatty changes, but no correlation between the severity of steatosis and the apoptosis was observed. The apoptotic hepatocytes did not show fatty changes. Apoptosis was seen in both mononuclear and binuclear hepatocytes.

Conclusion: PPC attenuates alcohol-induced apoptosis of hepatocytes; this protective effect may provide a potent mechanism against liver injury, possibly in association with PPC's antioxidative action.

Gastric Oxidation of Ethanol Accounts for Its First-Pass Metabolism. E. Baraona, C.S. Abittan, and C.S. Lieber. Alcohol Research and Treatment Center, Bronx VA. Medical Center, Bronx, NY; and Mount Sinai School of Medicine, New York, NY.

Oral alcohol consumption results in lower blood ethanol concentrations than intravenous infusion of the same dose, even when the latter is given at a rate equal to that of alcohol absorption. No such first pass metabolism (FPM) occurs when alcohol is administered by the duodenal or portal routes, which bypass the stomach. However, there is a controversy on whether the stomach can metabolize a sufficient amount of ethanol and to what extent gastric alcohol dehydrogenase (ADH) activity is responsible. To study this, we used 21 normal baboons, a species close to man. In 8 baboons, the aorta and the hepatic vein were cannulated percutaneously to estimate the splanchnic blood flow by the Fick principle (using indocyanine green) with an appropriate dose of alcohol. In 3 additional baboons, the aorta and the portal vein were cannulated non-occlusively to assess the conversion of ethanol to acetate *in vivo*. Thirty minutes after closing the abdomen, ^{14}C-ethanol (300 mg/kg as a 15% solution) was given intragastrically (IG) and ^{3}H-acetate was infused intravenously (IV) at a constant rate (1 mCi/mL). Simultaneous sampling of portal and arterial blood was carried out for 3 hours. The stomach content was then removed and alcohol (300 mg/kg) was given IV in 30 min. The ethanol left in the stomach at 3 hours was 73 ± 8 mg/kg. Michaelis-Menten analysis of the IV and IG ethanol curves revealed an FPM of 94 ± 11 mg/kg. The porto-arterial differences were negative for ^{3}H-acetate (indicating net extraction) and positive for ^{14}C-ethanol and ^{14}C-acetate (indicating net output). ^{14}C-acetate was calculated from the ^{14}C-radioactivity after exhaustive evaporation of ethanol in an alkaline solution. To calculate the production of acetate, its porto-arterial differences were multiplied by the portal plasma flow, considered to be 2/3 of the splanchnic plasma flow. Total acetate production (extraction plus net output) increased with time and continued beyond the 3-hour measurements; the production of acetate over the first 3 hours (82 ± 13 mg/kg) corresponded to a substantial fraction (87%) of the FPM of alcohol. In 10 animals, the capacity for gastric ADH to mediate ethanol oxidation was determined *in vitro*. The ADH activity of gastric mucosa (53 ± 14 mg/kg in 3 hours) was insufficient to account for the FPM, suggesting a contribution of a much higher activity in the esophagus or the participation of non-ADH systems.

Conclusion: The oxidation of ethanol by gastric ADH, measured *in vitro*, as well as the conversion of ethanol to acetate, measured *in vivo*, can account for most of the first pass metabolism of ethanol.

Cardiology

Have We Overestimated the True Value of Contrast Echo? A Quantitative Echo Study. T. Nahar, L. Croft, R. Shapiro, S. Buckley, M. Henzlova, J. Machac, J. Diamond, E. Stern, and M.E. Goldman. Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Harmonic (H) contrast (C) echo improves subjective LV endocardial border definition, which should translate into better quantification (quant) of LV ejection fraction (EF). However, C requires additional time, expense and an IV. To determine the incremental benefit of H and C imaging, we analyzed 50 2-D echoes obtained in four modes: fundamental (F), H, each with (C+) or without (C-) Optison® boluses. Each study was analyzed subjectively and biplane 2-D EF was blindly quantified and compared to radionuclear (RNC) EF. We defined an accurate 2-D EF to be = RNC EF ≤ ±5%.

	F:C–	F:C+	H:C–	H:C+
Visual Good	6	17	29	44
Poor	44	33	21	6
Quant ≤ ±5%	22	22	24	36
≥ ±5%	28	28	26	14

Subjective assessment of LV function and cavity was significantly better with addition of C and H imaging (Poor = ≥2 continuous segments poorly seen in 2 or 4 chamber view). If endocardium was visualized better by H+C, objective quant should reflect the improvement. C+ improved F quant (≤ ±5% to RNC) in 9 patients, while H:C+ improved quant in 21 patients. About 1/2 the benefit of H:C+ was from H alone. No parameter studied (age, sex, height, weight, LV, EF, LV size, blood pressure), predicted who benefited from H, C or both.

Thus, while the impact of H:C+ on quant is less than for subjective reading, H:C+ significantly improves quant compared to F:C+ or H:C–. Previous reports based on subjective readings may have overestimated the relative value of contrast echo.

Accurate Quantitative Echocardiography Requires Harmonic Contrast Imaging. T. Nahar, L. Croft, R. Shapiro, S. Buckley, M. Henzlova, J. Machac, J. Diamond, E. Stern, and M.E. Goldman. Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Quantitative LV ejection fraction (EF) measurement by 2-D echo is limited by subjective visual endocardial borders detection. Both harmonic (H) and contrast (C) echo provide better LV wall and cavity definition. To determine the incremental benefit of the newer technologies, we calculated modified Simpsons's biplane 2-D echo LV EF in 50 subjects, mean age = 48 ± 16 years, by fundamental (F) and H imaging, (Acuson Sequioa & ATL HDI 5000 CV) each with (C+), or without (C-) Optison® contrast boluses. Of the 50 echo studies, 44 qualified as technically difficult. Radionuclear (RNC) gated LV EF's done within 12 hours of the echo ranged from 18–72%, mean = 51 ± 17%. Blinded measurements were done on digitally stored images by 3 independent readers (Readers1-3) and were correlated with RNC EF's.

TABLE

Correlation of Echo LV EF with RNC Performed by 3 Independent Readers

	F:C–	F:C+	H:C–	H:C+
Reader 1	0.68	0.78	0.84	0.95
Reader 2	0.60	0.68	0.84	0.96
Reader 3	0.66	0.80	0.83	0.95
Mean	0.65	0.75	0.84	0.95
Bias ± S.D.	3.4 ± 15	5.0 ± 11	2.8 ± 9	– 1.2 ± 5

Contrast provided a similar increment in accuracy for F and H imaging, though the correlation of H alone was significantly better than F alone. Harmonics alone provided roughly ½ the advantage gained by contrast combined with harmonic imaging. Thus, quantitative echo is possible with newer imaging methods and is most accurate when harmonic imaging is performed with contrast.

Use of Microdialysis to Assess Interstitial Fluid Angiotensin II (Ang II) Concentration in the Rat Heart. F.M. Siri and S.A. Atlas. Hypertension Research Laboratory and Cardiology Section, Bronx VA Medical Center, Bronx, NY; and Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

There is controversy regarding the extent to which tissue Ang II levels are derived from circulating blood, since a number of tissues, including the heart, are in theory capable of local Ang II synthesis. Furthermore, the beneficial effects of drugs that block the renin-angiotensin system in cardiac disease extend to patients with normal circulating Ang II levels, leading some to postulate the existence of high tissue levels due to local synthesis.

Aim: To estimate cardiac interstitial fluid levels of Ang II using microdialysis in the intact beating rat heart *in situ*.

Methods: A dialysis probe (10 mm length, 0.5 mm OD) was inserted into the anterior myocardial wall (apex to base) of normal open-chest, pentobarbital-anesthetized rats. Krebs solution with 0.5% BSA was then perfused at 2 µL/min for 30–60 min periods, and samples were collected on ice into tubes containing EDTA. Blood samples were collected in EDTA prior to and following dialysate collection. Ang II in dialysates and in plasma was measured by radioimmunoassay following extraction on C_{18} SepPak cartridges. Further analysis of immunoreactive (ir) Ang II was performed using reversed-phase high performance liquid chromatography (rpHPLC) using a C_{18} column eluted isocratically with 22% acetonitrile in water.

Results: In initial studies (n = 5) irAng II levels averaged 72 ± 53 (mean ± SD) pg/mL in cardiac interstitial fluid and 51 ± 4 pg/mL in plasma. By rpHPLC analysis the irAng II in plasma and interstitial fluid had retention times (9.5 min) corresponding to that of authentic Ang II octapeptide. In subsequent studies somewhat higher interstitial fluid levels (as high as 500 pg/mL) were found on occasion, but generally in proportion to (and never more than double) that in plasma. Preliminary experiments indicate a prompt rise in both plasma and cardiac interstitial fluid Ang II levels during high-dose Ang II infusion.

Conclusions: These results contrast markedly with a report that interstitial fluid Ang II in the dog heart *in situ* is several orders of magnitude higher than plasma Ang II and is uninfluenced by exogenous Ang II infusion (Dell'Italia et al. J Clin Invest 1997; 100:253). The present results do not suggest such striking compartmentalization of Ang II in normal rat hearts. The data suggest that cardiac interstitial fluid Ang II is derived in part from the blood and/or that it is synthesized at a rate similar to that in blood. Further study is needed to determine whether interstitial fluid Ang II might be disproportionately elevated in the diseased heart.

Antihypertensive Efficacy of Omapatrilat: A Novel Vasopeptidase Inhibitor. S.A. Atlas[1], J. Baruth[1], P. Kumar[1], C. Rosendorff[1], R. Zusman[2], E. Adler[3], and E. Levy[3]. [1]Hypertension Unit and Cardiology Section, Bronx VA Medical Center, Bronx, NY; and Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY; [2]Massachusetts General Hospital, Boston, MA; and [3]Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ.

Omapatrilat, representative of a new class of antihypertensive agents termed "vasopeptidase inhibitors," is a single compound that simultaneously inhibits both neutral endopeptidase (NEP, K_i 8.9 nM) and angiotensin converting enzyme (ACE, K_i 6.0 nM). Inhibition of NEP slows the degradation of a number of endogenous vasodilatory and natriuretic peptide hormones, including the A- and B-type natriuretic peptides (ANP and BNP), bradykinin and adrenomedullin.

Aim: To determine the antihypertensive efficacy and safety of omapatrilat in patients with uncomplicated, mild-to-moderate essential hypertension.

Methods: Following a placebo washout period, subjects with seated diastolic blood pressure in the 95–110 mm Hg range were randomly assigned, in double-blind fashion, to receive either placebo (Pbo) or single daily doses of omapatrilat (Oma, 20–80 mg) for a 9-week period. Blood pressure was routinely measured at trough (i.e., 24 hours post dose) but also measured at peak (7 ± 1 hours post dose) on selected occasions.

Results: Administration of omapatrilat caused clear evidence of ACE inhibition (i.e., stimulation of plasma renin levels and decreases in plasma angiotensin II and aldosterone) as well as dose-dependent increases in urinary ANP and urinary cGMP excretion, consistent with effective NEP inhibition. Reductions in systolic (SBP) and diastolic (DBP) blood pressure were evident within 2–4 hours of administration and were sustained throughout the 9-week treatment period. Dose-dependent changes in trough BP were highly significant ($p < 0.001$ for all doses) compared to Pbo:

	Pbo	Oma 20 mg	Oma 40 mg	Oma 60 mg	Oma 80 mg
[n]	[99]	[111]	[104]	[107]	[296]
ΔSBP	–4.2	– 12.7	– 17.3	– 17.8	– 19.5
ΔDBP	–5.7	– 10.2	– 12.1	– 13.7	– 14.2

Peak reductions in SBP/DBP (–25.8/– 16.9 mm Hg for 80 mg) suggest an excellent trough-to-peak ratio. At 80 mg/day, trough DBP was <90 mm Hg in 69% of all subjects (83% of mild hypertensives).

Conclusions: Omapatrilat administered once daily is a well-tolerated and highly effective antihypertensive agent with a very high normalization rate for monotherapy. This and other studies suggest unusual efficacy at lowering SBP, and greater BP reduction compared to ACE inhibitors in African Americans, the elderly and other typically low-renin subsets. These features suggest that vasopeptidase inhibitors may provide a significant advance in the treatment of hypertension.

Marked Stimulation of Brain Natriuretic Peptide Gene Expression in Left Ventricular Myocardium of Rats with Chronic Ascending Aortic Banding. S.M. Dolgilevich, F.M. Siri, and S.A. Atlas. Hypertension Research Laboratory and Cardiology Section, Bronx VA Medical Center, Bronx, NY; and Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Brain natriuretic peptide (BNP) is a cardiac hormone with a longer biological half-life than atrial natriuretic peptide (ANP) and qualitatively similar natriuretic, diuretic and vasorelaxant activity. Although ANP is the major hormone secreted by the cardiac atria, both ANP and BNP are synthesized by ventricular muscle, and it has been suggested that plasma levels of BNP may provide a more reliable marker for congestive heart failure and ventricular hypertrophy.

Aim: To determine the extent to which the genes for BNP and ANP are transcriptionally regulated in a model of chronic pressure overload hypertrophy.

Methods: Samples of left (LV) and right (RV) ventricular myocardium were obtained from male Sprague-Dawley rats with ascending aortic constriction ($n = 10$) and normal controls ($n = 6$). Changes in gene expression were quantitated by Northern blot analysis using cDNA probes for ANP and BNP, and all values (presented as mean ± SD) were normalized to the level of expression of G3PDH measured simultaneously.

Results: Aortic constriction caused a marked increase in LV mass to body mass ratio after 5 – 7 days. This hypertrophy was accompanied by a greater than 30-fold increase in BNP expression in LV but not in RV. The level of BNP mRNA (arbitrary units, normalized to G3PDH expression) in LV rose from 0.05 ± 0.02 in controls to 1.45 ± 0.3 in rats with aortic constriction ($p < 0.01$), whereas levels in RV were no different in the two groups (0.22 ± 0.06 vs. 0.38 ± 0.09). Results were qualitatively similar for ANP expression in hypertrophied hearts, which was far greater in LV compared to RV (1.1 ± 0.5 vs. 0.09 ± 0.06 arbitrary units).

Conclusions: These results indicate that left ventricular synthesis of BNP is, like that of ANP, highly responsive to increases in systolic pressure. These findings suggest that these locally expressed cardiac hormones, which via stimulation of particulate guanylate cyclase (i.e., the type A natriuretic peptide receptor) are thought to have anti-mitotic actions, could play an important compensatory role in the progression of afterload-induced left ventricular hypertrophy.

Colocalization of Annexin V with Tissue Factor in Human Atherosclerotic Plaques — A New Thrombomodulatory Mechanism.

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Background: Annexin V is an anionic phospholipid binding protein with potent anticoagulant properties, which blocks tissue factor (TF) activity on membrane surfaces. Atherosclerotic plaques are rich in TF protein but even ruptured plaques are variable in their thrombogenicity. We examined the hypothesis that annexin V is present in plaques and may modulate plaque thrombogenicity following plaque rupture.

Design: Human atherosclerotic coronary, carotid, and aortic segments were fixed and processed for paraffin embedding. Sequential sections were stained with H&E, trichrome, and immunostained with specific antibodies against annexin V, macrophage CD68, smooth muscle cell a-actin, tissue factor, and von Willebrand factor.

Results: Normal arterial wall did not contain annexin V antigen except on endothelium. Lipid-rich atherosclerotic lesions contained focal areas of annexin V staining in the fibrous cap, shoulder and base regions. These areas were rich in intact macrophage foam cells. In sections of ruptured plaques, annexin V staining was evident at the base of the overlying thrombus associated with macrophages. All areas of annexin V staining also showed TF staining. Annexin V antigen was not associated with regions rich in smooth muscle cells.

Conclusion: Annexin V is present in plaques and colocalizes with macrophages and TF at the sites of rupture. Annexin V may be an important modulator of TF activity and thrombosis following plaque rupture.

*High-Resolution Magnetic Resonance Imaging of Complex *In Situ* Coronary and Aortic Atherosclerosis *Ex Vivo.*

S.G. Worthley[1], G. Helft[1], V. Fuster[1], Z.A. Fayad [1,2], J.I. Osende[1], J.T. Fallon[1,3], M. Roque[1], O.X. Rodriguez[1], A.G. Zaman[1], and J.J. Badimon[1]. [1]Cardiovascular Institute and Departments of [2]Radiology and [3]Pathology, Mount Sinai School of Medicine, New York, NY.

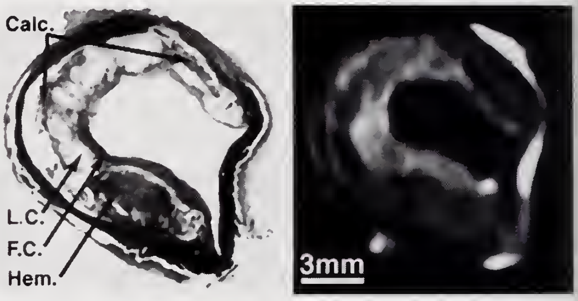
Acute coronary syndromes are the result of atherosclerotic plaque disruption and subsequent thrombosis. Atherosclerotic plaque composition is central in the pathogenesis of this process. Thus, there is a need for accurate imaging and characterization of atherosclerotic lesions. The porcine model is considered to closely resemble human atherosclerosis and has comparable coronary artery anatomy.

Aim: To validate *ex vivo* magnetic resonance imaging (MRI) characterization of atherosclerotic lesions from *in situ* coronary arteries and aortas in a novel model of complex porcine atherosclerosis and validate this with histopathology.

Methods: Coronary and aortic atherosclerosis was induced in Yucatan mini-swine ($n = 4$) by a combination of atherogenic diet (2% cholesterol) for 6 months and sequential balloon injury. All coronary arteries were imaged *ex vivo* on the intact heart, preserving the curvature of their course. The aortas also underwent MRI. The MR images were correlated with the matched histopathology sections for both the coronary arteries ($n = 54$) and the aortas ($n = 43$).

Results: Mean wall thickness for the coronary arteries ($r = 0.94$, slope = 0.81) and aortas ($r = 0.94$, slope = 0.81) was accurately determined by MR imaging ($p < 0.0001$). MR imaging accurately characterized complex atherosclerotic lesions, including calcified (Calc.), lipid-core (L.C.), fibro-cellular (F.C.) and hemorrhagic (Hem.) regions (see figure of aorta).

Conclusions: MRI accurately quantifies and characterizes coronary and aortic atherosclerotic lesions in this experimental porcine model of complex atherosclerosis. This model may be useful for future studies of MRI of complex atherosclerosis *in vivo*.



High-Resolution *In Vivo* Magnetic Resonance Imaging of Experimental Coronary Artery Plaques.

S.G. Worthley[1], G. Helft[1], V. Fuster[1], Z.A. Fayad[1,2], O.X. Rodriguez[1], J.T. Fallon[1], A.G. Zaman[1], and J.J.Badimon[1]. [1]Cardiovascular Institute, and Departments of [2]Radiology, and [3]Pathology, Mount Sinai School of Medicine, New York, NY.

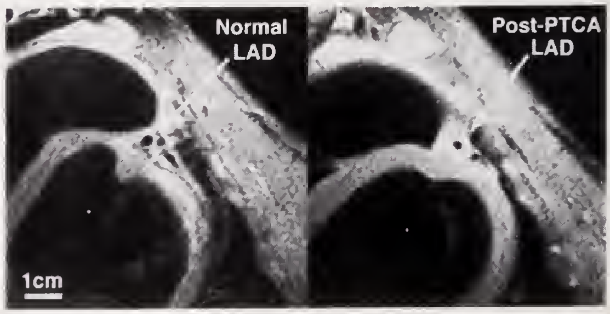
Atherosclerotic plaque composition modulates its vulnerability and thrombogenicity. *In vivo* magnetic resonance imaging (MRI) has been used to characterize and quantify non-coronary lesions. The major limitation of MRI has been the inability to translate this to atherosclerotic lesions within the coronary arteries. This is due to cardiac and respiratory motion artifacts, as well as the size and non-linear course of these arteries.

Aims: To develop and validate a novel MRI technique in a clinical 1.5 Tesla system that permits, for the first time, high-resolution imaging and characterization of lesions in coronary arteries in a porcine model.

Methods: Lesions were induced in Yorkshire albino swine ($n = 5$) in all 3 major epicardial coronary arteries with balloon angioplasty. *In vivo* MRI was performed 4 weeks post-angioplasty, with a standard phased array surface coil in a clinical 1.5 Tesla MR system (GE). A unique double inversion recovery fast spin echo sequence was used, allowing high-resolution (0.39 – 0.48 mm in-plane resolution, slice thickness 5 mm) proton density and T2 weighted imaging, while nulling flow signal. The figure shows an MR image of a fibrocellular coronary lesion in the left anterior descending artery (LAD). Included is an MR image of the coronary wall of a normal LAD for comparison. Cardiac gating and breath-holding (<30 seconds/image) was used to suppress motion artifacts.

Results: An excellent correlation ($p < 0.001$) between matched *in vivo* images and histopathology sections ($n = 24$) was observed for mean wall thickness ($r = 0.93$, slope = 0.96). Intralesion hematoma was readily identified from the fibrocellular components with MRI.

Conclusions: The non-invasive characterization of coronary lesions using MRI raises new therapeutic possibilities allowing risk stratification for plaque disruption and selection of therapeutic strategies based on plaque composition.



Do Patients with Primary Autonomic Failure Have Target Organ Damage? T. Vagaonescu[1], D. Saadia[2], A. Butkevich[1], R. Phillips[1], and H. Kaufman[2]. [1]Hypertension Section, Cardiovascular Institute, and [2]Department of Neurology, Mount Sinai School of Medicine, New York, NY.

The most apparent problem in patients with primary autonomic failure (PAF) is orthostatic hypotension. However, this occurs only when the patient is sitting or standing. When supine, most patients with PAF have hypertension. Whether the supine hypertension, occurring only a few hours a day, is associated with target organ damage is unknown.

Aim: To assess if patients with PAF have left ventricular hypertrophy (LVH) and if the LVH correlates with their 24-hour blood pressure profile.

Methods: Ten patients with PAF (all treated with fludrocortisone and midodrine) were matched for sex and age with 10 normotensives (NT) and 10 essential hypertensives (EH). Ambulatory blood pressure monitoring and LV mass measurement (echocardiography) was performed in all patients.

Results: PAF patients had 24-hour and daytime systolic BP (DSBP) within normotensive range, but their nighttime SBP (NSBP) and LV mass index (LVMI) were similar to those of EH. PAF patients had a reversed nocturnal BP change when compared to EH and NT (Table). LVMI correlated with the 24-hour SBP in PAF patients (r = 0.70; p = 0.01).

	PAF (x ± SD)	NT (x ± SD)	EH (x ± SD)
24-hr SBP	128 ± 15	125 ± 5	140 ± 91,2
DSBP	125 ± 16	128 ± 5	142 ± 81,2
NSBP	138 ± 181	115 ± 7	135 ± 141
DiffSBP	– 12 ± 171	13 ± 5	8 ± 7
LVMI	74 ± 291	40 ± 13	58 ± 11

Diff SBP = DSBP-NSBP

[1]p < 0.001 vs. NT; [2]p < 0.01 vs. PAF; [3]p < 0.001 vs. NT and EH (ANOVA)

Conclusions: Although PAF patients had 24-hour SBP within normotensive range, their NSBP and LVMI were significantly higher than in NT and similar to EH. The increased NSBP in patients with PAF is responsible, most likely, for their LVH. This finding may have further therapeutic implications.

Contrast Harmonic Echo Is the "Great Equalizer" for Quantitative Echo. L. Croft, T. Nahar, R. Shapiro, S. Buckley, M. Henzlova, J. Machac, J. Diamond, E. Stern, and M.E. Goldman. Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

Accurate LV ejection fraction (EF) calculation by 2-D echo requires experience in endocardial border detection. Contrast (C) and harmonic (H) imaging, which both enhance cavity delineation, may improve LV EF quantification by less experienced users. Thus, 2-D imaging was performed on 33 patients in 4 different modes: fundamental (F), H (Acuson Sequoia & ATL HDI 5000 CV) with (C+) and without (C–) Optison® contrast bolus injections. Radionuclear (RNC) gated EF's were obtained within 12 hours of the echo, and ranged from 18–72% (mean = 51 ± 16%). 2-D biplane EF's (modified Simpson's), calculated by both a junior FELLOW and experienced echocardiologist (EXPERT) independently and blinded to RNC, were correlated with RNC EF.

TABLE

Correlation of Echo to RNC LV EF Measurements by Expertise

	F:C–	F:C+	H:C–	H:C+
FELLOW	0.59	0.68	0.69	0.91
Bias	–2.8 ± 13.8	–2.8 ± 12.2	–3.6 ±12.6	–3.8 ± 6.9
EXPERT	0.66	0.80	0.83	0.95
Bias	– 1.3 ± 13.9	–5.3 ± 11.1	–3.9 ± 10.3	–2.6 ± 5.8

Contrast and harmonic modes each significantly improved the EXPERT reader's accuracy, while only when harmonics and contrast were used together did FELLOW's EF's reach acceptable results. Thus, contrast harmonic imaging may empower less experienced users with the ability to assess and quantify LV function as accurately as more experienced echocardiologists.

Coronary Angiographic Findings and Effect of Coronary Artery Disease on Left Ventricular Function among Minorities at North General Hospital. J. Desueza and M. Maw. Cardiology Section, Department of Medicine, North General Hospital, New York, NY.

Objective: To evaluate the difference in coronary angiographic findings among African Americans and Hispanics in a community hospital, and correlate the effects of coronary artery disease on left ventricular function.

Design: Retrospective cohort study based on reviewing hospital reports of coronary angiographies performed at four tertiary teaching hospital in the City of New York, from February 1992 to June 1998.

Setting: A private voluntary community hospital located in East Harlem, New York.

Patients: The study included 241 patients, consisting of African Americans (n = 178) and Hispanics (n = 63) who underwent coronary angiography at four different specialized facilities. Also echocardiograms done at North General Hospital were reviewed. Statistical analysis was done with Stata Quest 4 software, Chi square test used for categorical variables and Student test for continuous variables. A p value ≤ 0.05 was used to identify statistically significant results.

Results: More African Americans underwent coronary angiography as compared to Hispanics (74% vs. 26%). Also noted is predominance of females as compared to males (56.8% vs. 43.2%). Coronary artery disease (CAD), defined as 70% or greater reduction in cross-sectional area of a major coronary artery, was found in 46% of African Americans (AA) and 56% of Hispanics (Hisp); but difference was not statistically significant (p = 0.1). Also, when comparison by multivessel (2 to 3 vessels affected) was done, no significant difference was found (AA: 31% vs. Hisp: 34%).

After exclusion of patients with valvular disease, a 50% increase in left ventricular mass (LVM) was found in Hispanics with CAD compared with those without CAD (158 g/m^2 vs. 104 g/m^2, p = 0.003).

Also found was a 23% decrease in ejection fraction (EF) (41% vs. 53%). Similar findings were observed in the African-American population but these were not as striking as in the Hispanic population. There was a 10% decrease in EF (CAD: 48% vs. no CAD: 52%, p = 0.01) and 7% increase in LVM (137 g/m^2 vs. 127 g/m^2, p = 0.4).

Conclusion: There was no significant difference in angiographic findings among African Americans and Hispanics, although it was significant by gender (males > females). The Hispanic population had a greater significant worsening of the left ventricular function, as measured by ejection fraction and increased left ventricular mass, when coronary artery disease was present, as compared to African Americans. These findings may partially explain the slower decrease in coronary artery disease mortality among Hispanics than among African Americans. Also, previous studies (5) have found a worse type of left ventricular hypertrophy (concentric hypertrophy) among Hispanics, a finding confirmed in our present study. The above findings indicate the need for more aggressive therapy in this ethnic group, as it is well known that they have a higher incidence of obesity, dyslipidemia and diabetes mellitus (6).

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Imaging of Atherosclerotic Lesions with ^{18}FDG PET in Rabbits. G. Helft[1], S.G. Worthley[1], Z.Y. Zhuang[2], C. Tang[3,4], O.J. Rodriguez[1], J.T. Fallon[5], Z.A. Fayad[1,4], J. Machac[2], M. Buchsbaum[3], V. Fuster[1], and J.J. Badimon[1]. [1]Cardiovascular Institute, and Departments of [2]Nuclear Medicine, [3]Neuro-Psychiatry, [4]Radiology, and [5]Pathology, Mount Sinai School of Medicine, New York, NY.

Acute thrombosis on disrupted atherosclerotic plaques plays a key role in the onset of acute coronary syndromes and atherosclerosis progression. Macrophages are critical in plaque vulnerability and modulate its thrombogenicity upon rupture. Quantification of macrophage accumulation would assist in the determination of plaque vulnerability. ^{18}FDG has been reported to have high affinity for macrophages within tumors. Given its good imaging characteristics, ^{18}FDG PET could be a useful non-invasive *in vivo* imaging technique for quantifying macrophage content within atherosclerotic plaques.

Aims: To correlate uptake of ^{18}FDG with histopathological macrophage accumulation in atherosclerotic lesions.

Methods: Normal ($n = 3$) and atherosclerotic rabbits ($n = 6$) were studied. Aortic atherosclerosis was induced by a combination of cholesterol-rich diet (0.2% cholesterol for 9 months) and double balloon denudation with a 4 Fr. embolectomy catheter. *In vivo* imaging was performed with a GE brain PET camera 30 min after injection of 34 – 72 MBq of ^{18}FDG. Macrophage area was estimated by RAM-11 positive staining on histopathology and uptake of the ^{18}FDG by the thoracic aorta using standard uptake values (SUVs) and ratio of aortic-to-cardiac uptake were analyzed. ^{18}FDG uptake and RAM-11 antibody stainings were averaged for the proximal 4 cm of the thoracic aorta of each rabbit.

Results: Atherosclerotic aortas showed an intense focal uptake of ^{18}FDG. A highly significant correlation ($r = 0.71$, $p < 0.05$) was observed between macrophage-positive areas assessed by histopathology and ^{18}FDG uptake by SUV. The aortic-to-cardiac uptake ratio also correlated significantly ($r = 0.81$, $p < 0.001$) with the macrophage area.

Conclusions: Thus, ^{18}FDG PET quantifies *in vivo* macrophage burden within aortic atherosclerotic plaque. This promising imaging tool could serve to serially monitor changes in the cellular content of atherosclerotic lesions and thus stratify patients at risk for plaque rupture.

Benefits of Clopidogrel on Inhibition of Platelet Aggregation and Activation in Patients on Chronic Aspirin Therapy. G. Helft, J.I. Osende, O.J. Rodriguez, S.G. Worthley, A.G. Zaman, E. Lev, S. Palencia, V. Fuster, J.J. Badimon, and J.H. Chesebro. Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY.

The antiplatelet drug clopidogrel has been shown to be at least as effective as aspirin in clinical trials. The additive antiplatelet effects of the two agents are yet to be accurately quantified in patients with known cardiovascular disease.

Aims: To compare platelet aggregation in patients with cardiovascular disease ($n = 15$) on chronic aspirin (325 mg per day) before and after one week of additional clopidogrel (75 mg per day).

Methods: Assessment of platelet function and activation was performed at baseline (aspirin alone) and after 7 days on clopidogrel (plus aspirin). Thus, each patient served as their own control. Platelet aggregation was determined in platelet-rich plasma (PRP) using ADP (10, 5, 2.5 µM) and collagen (5, 3 mg/mL). Platelet activation was assessed by flow cytometric determination of ADP-induced (0.12 and 0.6 µM) platelet surface binding of fibrinogen.

Results: There was a significant decrease ($p < 0.001$) in platelet aggregation at all doses of ADP tested, after 7 days of additional clopidogrel therapy. The respective mean percentage decreases in ADP-induced platelet aggregation were 26.6% (10 µM), 32.8% (5 µM) and 41.6% (2.5 µM). Interestingly, we also observed an inhibitory effect on collagen-induced platelet aggregation ($p < 0.01$) after 7 days of additional clopidogrel therapy, and at all doses tested. The respective mean percentage decreases in collagen-induced platelet aggregation were 18.6% (5 mg/mL) and 24.8% (3 mg/mL). Platelet activation was also significantly decreased ($p < 0.01$) after the addition of clopidogrel. ADP-induced fibrinogen binding to glycoprotein IIb/IIIa receptors was significantly reduced by clopidogrel: 26.81% to 6.89% with 0.12 µM; 54.56% to 23.88% with 0.6 µM. There were no hemorrhagic complications noted during the study period.

Conclusions: The addition of clopidogrel to chronic aspirin therapy significantly increases inhibition of platelet aggregation and activation. This data supports the added clinical benefit of combining clopidogrel and aspirin in patients with cardiovascular disease.

Non-invasive Magnetic Resonance Imaging Detects and Quantifies Atherosclerotic Plaque Components in Rabbits. G. Helft[1], S.G. Worthley[1], V. Fuster[1], Z.A. Fayad[1,2], J.I. Osende[1], J.T. Fallon[1,3], A.G. Zaman[1], M. Roque[1], O.J. Rodriguez[1], and J.J. Badimon[1]. [1]Cardiovascular Institute and Departments of [2]Radiology and [3]Pathology, Mount Sinai School of Medicine, New York, NY.

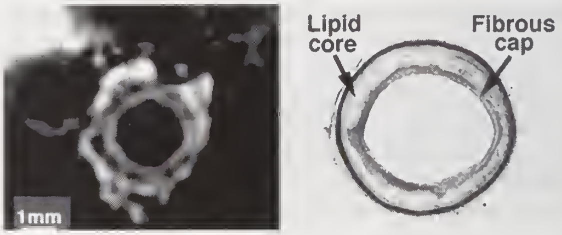
Non-invasive, high-resolution MRI may be used to serially study the effects of therapeutic interventions on atherosclerotic plaque stabilization *in vivo*. This stabilization results from changes in lesion composition.

Aims: To validate for the first time the ability of MRI to quantify lipidic and fibrotic components of lesions in a rabbit model.

Methods: Thoracic and abdominal aortic atherosclerosis was induced in New Zealand white rabbits ($n = 15$) by a combination of atherogenic diet (0.2% cholesterol) and double balloon aortic denudation. MRI of the entire aorta was performed in a clinical 1.5 T system (GE). Fast spin echo sequences were obtained with in-plane resolution of 0.35 mm and slice thickness of 3 mm. T2 (TR/TE 2300/55 msec) and proton density weighted (PDW) images (TR/TE 2300/17 msec) were acquired. After euthanasia, histopathological sections were matched with MR images.

Results: A significant correlation ($p < 0.05$) between MRI and histology (Oil Red O staining) for analysis of lipidic (low signal on T2w, $r = 0.81$) and fibrous (high signal on T2w, $r = 0.86$) areas was observed. Mean wall thickness correlated significantly ($p < 0.001$) between MRI and histology (CME) for the thoracic ($r = 0.75$) as well as the abdominal aorta ($r = 0.87$) (see Figure). Despite the cardiac and respiratory motion, we found that the thoracic aorta was relatively spared from these artifacts.

Conclusions: Non-invasive, high-resolution MRI allows qualitative and quantitative analysis of aortic atherosclerotic composition in this rabbit model. The *in vivo* feasibility of this technique permits the serial analysis of therapeutic strategies for atherosclerotic plaque stabilization.



Early Inflammatory Response and Intimal Hyperplasia after Mouse Femoral Artery Endothelial Denudation. M. Roqué[1], J.T. Fallon[1,2], J.J. Badimon[1], M.B. Taubman[1], and E.D. Reis[3]. [1]Cardiovascular Institute, and Departments of [2]Pathology and [3]Surgery. Mount Sinai School of Medicine, New York, NY.

Techniques of arterial injury commonly used in animals to mimic endovascular procedures are not suitable for small-sized mouse arteries. This has limited the examination of the response to arterial injury in genetically modified mice. We have developed a reproducible model of transluminal arterial injury in the mouse that results in substantial intimal hyperplasia.

Aims: To examine early inflammatory events and the time course of the proliferative response after injury.

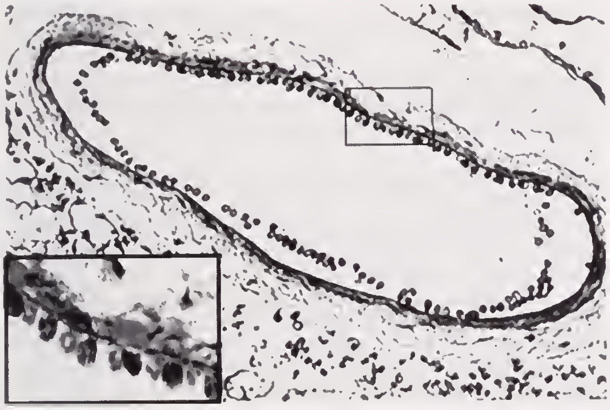
Methods: C57BL/6 mice ($n = 100$) underwent denudation of the femoral artery by passage of an 0.01" angioplasty guidewire.

Results: After injury, intimal hyperplasia was noted in 10% of arteries at 1 week, 88% at 2 weeks, and 90% at 4 weeks. Regenerated endothelium covered 7% of the luminal surface at 24 hours, 28% at 1 week, 49% at 2 weeks, and 91% at 4 weeks. The intima-to-media ratio reached 1.1 ± 0.1 at 4 weeks. Morphometry data are summarized in the Table.

	1 hour	24 hours	1 week	2 weeks	4 weeks
n (arteries)	10	10	20	66	58
Intimal hyperplasia (%)	0	0	10	88	90
Endothelial regeneration (%)	0	7 ± 0.2	28 ± 3.7	49 ± 1.7	91 ± 1.8
I/M ratio	0	0	0.2 ± 0.05	0.5 ± 0.1	1.1 ± 0.1

One hour after injury, the denuded surface was covered with platelets and leukocytes, predominantly neutrophils (see Figure), associated with the presence of P-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). These adhesion molecules were absent in the underlying media and normal endothelium.

Conclusions: These findings suggest that early leukocyte adhesion to the injured surface may be promoted by functional adhesion molecules derived from the circulation. Used in genetically modified mice, this model will be valuable for studying the role of specific molecules in mediating the arterial response to injury.



Clinical Immunology

Thyroid Amyloidosis in a Patient with Common Variable Immunodeficiency.

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Amyloidosis in patients with common variable immunodeficiency (CVI) is rare. There have been fewer than 20 reported cases of amyloidosis in patients with CVI or agammaglobulinemia. The pathogenesis of amyloidosis in CVI is not clear but may be due to recurrent infections triggering the deposition of amyloid A (AA) protein in the tissues. We report a 43-year-old male with recurrent pneumonia and bronchiectasis due to CVID on intravenous gammaglobulin (IVIG) replacement. He was diagnosed at the age of 8 years with low serum IgG, IgA and IgM. He was initially treated with intramuscular injections of immunoglobulins. He was switched to IVIG in 1980 but still had pneumonias, although less frequently. He was on IVIG every 3 weeks and rotating antibiotics when he presented with large, painful neck mass of 1-week duration. Computed tomography (CT) scan showed a large loculated mass in the thyroid, which was encroaching on the airway. He underwent total thyroidectomy that revealed an enlarged thyroid with amyloidosis along with focal necrosis and abscess formation. Immunohistochemical staining was positive for AA protein, suggesting that chronic lung infection and bronchiectasis may be the etiology of the amyloidosis. Since the most common mode of presentation of amyloidosis in hypogammaglobulinemic patients is with nephrotic syndrome, 24-hour urine protein measurement was done; it showed 2 gm/day proteinuria. Serum creatinine was slightly elevated to 1.6 mg/dL. The patient had normal renal ultrasound and no evidence of cardiac involvement seen on echocardiogram. To determine the systemic involvement, abdominal fat pad biopsy was done, but Congo red staining of the specimen was negative. Patient is to be started on colchicine, which may prevent further progression of his renal disease. This is the first reported case of CVI patient presenting with thyroid amyloidosis. His presentation may allow slower progression of his renal disease.

A Mouse Model of Cow Milk Hypersensitivity Induced by Oral Sensitization and Challenge.

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Cow milk is one of the leading causes of food allergy in children. The lack of suitable animal models has hampered the development of new therapeutic strategies for treating cow milk allergy (CMA). Utilizing cholera toxin (CT) and cow milk (CM) proteins, we developed a mouse model of IgE-mediated CM hypersensitivity. Three-week-old C3H/HeJ mice were sensitized orally with various doses of homogenized cow milk (HCM) and CT, and boosted 5 times at weekly intervals. Sera were collected weekly and CM-specific IgE, IgG1 and IgG2a antibodies were quantified by ELISA. Levels of CM-specific IgE were significantly increased at week 3 and peaked 6 weeks following initial sensitization. Mice were challenged orally with CM on week 6.

Symptoms of systemic anaphylaxis were evident within 15 – 30 minutes of challenge. Mice sensitized with a medium dose (1 mg/g body weight) of HCM had the highest levels of serum IgE and experienced the most severe systemic anaphylactic reactions. Plasma histamine levels increased significantly following challenge, indicating that mast cell activation was involved in the induction of anaphylaxis in this model. Intestinal permeability to casein was also found to increase. Th2 responses were likely to be responsible for the development of CM hypersensitivity in this model, since *in vitro* stimulation of spleen cells from CM-allergic mice lead to significant secretion of IL-4 and IL-5, but not IFN. These results demonstrated that under certain conditions, oral sensitization and challenge of mice can induce IgE-mediated CM allergy, which closely mimics clinical features seen in humans. This model should provide a useful tool for evaluating immunopathogenic mechanisms involved in CM allergy and for exploring novel therapeutic approaches.

The Inhibitory Receptor Complex CD94/NKG2A May Down-Regulate the Activation of IEL by gp180.

L.S. Toy[1], B. Jabri-Bendelac[2], N. Cerf-Bensussan[3], N.A. Campbell[1], and L. Mayer[1]. [1]Division of Clinical Immunology, Department of Medicine, Mount Sinai School of Medicine, New York, NY; [2]Department of Microbiology, Princeton University, Princeton, NJ; and [3]Department of Pediatric Gastroenterology, Hôpital Necker, Paris, France.

We have previously demonstrated that gp180, an intestinal epithelial cell (IEC) surface glycoprotein, is important in the activation of CD8+ suppressor T cells and results in the activation of CD8-associated p56lck. Furthermore, we have shown that gp180 can associate with non-classical class I restriction elements. The non-classical class I molecule HLA-E binds to the natural killer (NK) cell inhibitory receptor complex CD94/NKG2A, resulting in the inhibition of T cell activation and NK killing. Up to 30% of intestinal intraepithelial lymphocytes (IEL) express this complex. In addition, others have documented that IEL can recognize non-classical class I molecules.

Aim: In previous studies, we have shown that, in contrast to peripheral blood T cells, IEL neither proliferate nor manifest p56lck activation when co-cultured with IEC. We sought to determine whether one component of this failure to activate p56lck might occur through CD94/NKG2A.

Methods: CD94 high/NKG2A+ and CD94 low/NKG2A- clones derived from normal TCRab+ CD8+ IEL were incubated with anti-CD8 mAbs or gp180. Activation of lck was determined by lysis of T cells followed by an anti-phosphotyrosine Western blot.

Results: Unlike freshly isolated IEL, in which activation of CD8-associated p56lck is down-regulated in this system, all IEL clones could be activated (p56lck phosphorylation) with anti-CD8 mAbs. Thus in the absence of IEC, CD8 mediated signal transduction can be restored. However, when these same clones were co-cultured with gp180, p56lck phosphorylation was only noted in the CD94 low/NKG2A- cells.

Conclusions: These results may indicate a direct interaction of gp180 with the C-lectin like CD94 molecule, or alternatively, gp180 associates with a non-classical class I molecule which interacts with the CD94/NKG2A complex, activating the tyrosine phosphatases SHP-1 and SHP-2. This complex interaction may prevent T cell activation and potentially inhibit cytolytic T cell function in the epithelium.

Endocrinology

Prolongation of Thyroiditis in the Murine Post-Partum Period.

M. Imaizumi[1], A. Pritsker[1], P. Unger[2], and T.F. Davies[1]. Departments of [1]Medicine and [2]Pathology, Mount Sinai School of Medicine, New York, NY.

Many human autoimmune diseases, including autoimmune thyroid disease, are affected by immune changes during pregnancy and the postpartum period. Moreover, the severity of autoimmune diseases may be associated with a disparity in HLA class II antigens between mother and fetus. To investigate the influence of a disparity in HLA class II between mother and fetus on the development of thyroglobulin (Tg) induced experimental autoimmune thyroiditis (EAT), we examined the intrathyroidal histological changes of CBA/J (H-2k) female mice which were mated with BALB/c (H-2d) males. Fifty-six (56) female CBA/J mice were immunized with IV Tg (50 :g). Three hours later, they were injected with 20 :g of lipopolysaccharide (LPS). Twenty-six (26) female Tg immunized mice were mated with BALB/c males one week after the second immunization and were sacrificed in late pregnancy, 2 weeks post-partum and 5 weeks post-partum. Thyroid histology by H&E staining was graded as follows; 0.5: small focal areas of inflammatory cells; 1.0: focal collections of mononuclear cells with some follicular destruction; 2.0: diffuse infiltration of thyroid follicle involving approximately 40% or less of thyroid tissue examined; 3.0: destruction of 40% to 80% of thyroid tissue; 4.0: destruction of more than 80% of thyroid tissue. There was no statistical difference in the rate of development of thyroiditis between the non-pregnant group and late pregnancy (5 weeks after first immunization); the percentage being 50% and 60%, respectively. However, 75% of the pregnancy group maintained thyroiditis at 5 weeks post-partum (10 weeks after first immunization), compared with only 20% of the non-pregnant group ($p < 0.02$ by chi-square test). The average thyroiditis grade at 5 weeks post-partum was 0.44 in the pregnant group and 0.10 in the non-pregnant group. We concluded that the severity of EAT was prolonged during the postpartum period in this mouse model.

Evidence for CC Chemokine Receptor #5 (CCR5) Involvement in Homing of T Cells to the Thyroid Gland. M. Imaizumi[1], A. Pritsker [1,2], P. Unger[2], and T.F. Davies[1]. Departments of [1]Medicine and [2]Pathology, Mount Sinai School of Medicine, New York, NY.

Lymphocytic infiltration is associated with secretion of chemokines and expression of their receptors, as well as various adhesion molecules, at the sites of autoimmune disease. The CC chemokine receptor #5 (CCR5) has been described as one of the chemokine receptors which induce lymphocyte chemotaxis and may also be a marker of Th1 type (cytotoxic) T cells. To investigate the expression of CCR5 in autoimmune thyroiditis, we examined CCR5 expression by intrathyroidal lymphocytes and cultured spleen cells from thyroglobulin (Tg) induced experimental autoimmune thyroiditis (EAT) in which cytotoxic T cells are known to predominate. CBA/J female mice were immunized intravenously with 50 µg of murine Tg and 20 µg of lipopolysaccharide (LPS) at the beginning of the study, and one week later. Animals were sacrificed 5 weeks after the first immunization and control mice were injected with only LPS. Histological assessment of the mouse thyroids at week 5 showed a mean grade of 0.75. In animals in which EAT was induced, 20 – 40% of intrathyroidal lymphocytes expressed CCR5 as determined by immunohistochemical analysis (by antibody CKR5, Santa Cruz, CA). No CCR5 positive cells were observed in control thyroids. In contrast, spleen cells, even when stimulated *in vitro* by concanavalin A, were <5% CCR5 positive by flow cytometry. These results indicated that the intrathyroidal lymphocytic infiltrate in EAT was made up of primarily Th1 cells which expressed CCR5. We conclude that the low percentage of CCR5 positive spleen cells was highly suggestive evidence that CCR5 is the thyroid lymphocyte homing molecule.

An Unusual Variant of the Mouse TSH-Receptor Lacking the First Transmembrane Segment and Intracellular Loop. C. He, P. Graves, and T. Davies. Division of Endocrinology and Metabolism, Mount Sinai School of Medicine, New York, NY.

We have recently employed recombinant mouse TSHR ectodomain as an immunogen for the induction of murine Graves' disease (GD). The immune response, however, produced TSHR blocking rather than stimulating autoantibodies (Clin Exp Immunol 1998, 113:111). In order to employ intact, full-length, mouse TSHR to provide a more appropriate immunogen, we set about cloning the mouse TSHR. Northern analysis using a human TSHR probe indicated the presence of multiple mTSHR mRNA splicing variants, including 4.3 Kb, 3.5 Kb, 2.9 Kb and 1.0 Kb. Using CBA/J thyroid mRNA we observed that PCR-amplified mTSHRs contained the expected variety of product lengths. Cloning and sequencing, likewise, revealed both full-length clones and clones which lacked portions of the cDNA. One of the most unusual clones lacked the coding region for the first transmembrane segment and the first intracellular loop. Using specific primers for this receptor variant, we confirmed the presence of this variant in normal mouse thyroid mRNA, and semi-quantitative analysis suggested that the variant made up ~ 10% of mTSHR transcripts. The cDNA was subcloned into the pCDNA expression vector under the CMV promoter and used to establish stable CHO transfectants. The resulting cells showed no TSHR signal transduction as evidenced by the lack of cyclic AMP generation. In conclusion, the normal mouse thyroid cell contains many different TSHR transcripts, including variants which fail to effect signal transfer. Whether normal and abnormal receptor structures interact or not in the control of thyroid function deserves exploration.

Lymphocytic Hypophysitis: A Case Report and Review of the Literature. J. Najjar, C. Asta, and R. Rizzo. Department of Medicine, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Lymphocytic hypophysitis (LH) is a rare autoimmune pituitary disorder characterized by pituitary enlargement and insufficiency. One hundred twenty-eight cases, many without histological evidence, have been reported since 1962, occurring predominantly in women during late pregnancy or the postpartum period.

We describe a case of a 19-year-old female who presented, 2 months after a spontaneous vaginal delivery, with headaches and bilateral visual field deficits. On physical examination, pertinent findings included bilateral dilated pupils, absent pupillary reflex in the left eye, blindness of the left eye and restricted visual field to only the upper nasal quadrant of the right eye. Neuroimaging with computed tomography (CT) scan and magnetic resonance imaging (MRI) showed a large, homogeneously enhancing pituitary tumor. The patient underwent transeptal transphenoidal subtotal resection of the mass. The pathology report confirmed LH. The patient's vision improved dramatically postoperatively, but the patient developed diabetes insipidus.

The epidemiology, pathogenesis, clinical presentation and natural history of LH are discussed, as well as the importance of including LH in the differential diagnosis of females with pituitary enlargement presenting in the peripartum period. A review of the management of this entity with corticosteroid therapy versus surgical treatment will be presented.

Prostaglandin E_2 Upregulates Vascular Endothelial Growth Factor Expression in Prostate Cancer Cells. X.H. Liu, A. Kirschenbaum, S. Yao, J.F. Holland, and A.C. Levine. Departments of Medicine and Urology, Mount Sinai School of Medicine, New York, NY.

We have previously demonstrated that androgens upregulate vascular endothelial growth factor (VEGF) expression in human prostate cells. Most prostate cancers become androgen-insensitive, and we postulate that hypoxic upregulation of VEGF *in vivo* plays an important role in tumor progression. We further hypothesize that hypoxic effects on VEGF expression are mediated by cyclooxygenase-2 (COX-2), and one of its major derived products, prostaglandin E_2 (PGE_2). PC-3 ML human prostate cancer cells (a highly invasive subline of androgen-insensitive PC-3 cells) were treated with 100 µM cobalt chloride (to induce hypoxia) ± NS398 (a selective COX-2 inhibitor) and/or $PGE_2$2, and the effects on VEGF and COX-2 mRNA and protein expression measured by Northern blot, Western blot and ELISA. Hypoxia upregulated both COX-2 (5 fold induction beginning at 16h) and VEGF (7-fold induction beginning at 20h) protein expression. Hypoxia also resulted in a 4-fold increase in PGE_2 secretion at 48h. The hypoxia-driven increases in VEGF mRNA and protein expression were blocked in a dose-dependent fashion by the selective COX-2 inhibitor, NS398 (10 – 100 µM) for 3 days. Further addition of the COX-2 product, PGE_2, completely restored the VEGF response to hypoxia in the presence of COX-2 inhibition. These data indicate that COX-2 and its major derived product PGE_2 are mediators of hypoxic effects on VEGF expression. COX-2 inhibitors may serve as antiangiogenic therapy for androgen-insensitive human prostate cancers.

Neurological, Ethnic, and Gender Considerations in the Oral Glucose Tolerance of Persons with Chronic Immobilization. W. Bauman[1,2], R. Adkins[3], A. Spungen[1,2], B. Kemp[3], and R.Waters[3]. [1]Mount Sinai School of Medicine, New York, NY; [2]Bronx VA Medical Center, Bronx, NY; and [3]Rancho Los Amigos Medical Center, Downey, CA.

In the general population, abnormal oral carbohydrate tolerance is associated with increased risk for coronary heart disease. A few reports have demonstrated that persons with spinal cord injury (SCI) have abnormal glucose tolerance, hyperinsulinemia and insulin resistance.

Aims: This study addressed the overall effects of SCI on carbohydrate metabolism in subgroups of subjects categorized by level of lesion, gender and ethnicity.

Methods: A standard 75 g oral glucose tolerance test was performed on 201 subjects with SCI (169 male and 32 female; 54 white, 28 black, 114 Latino, and 5 Asian/American Indian) who were outpatients being seen for routine annual physical examination at Rancho Los Amigos Medical Center.

Results: The results were reported as mean ± SEM. The age of the group was 39.1 ± 0.77 years, duration of injury, 14.0 ± 0.65 years, and body mass index (BMI), 25.3 ± 0.43 kg/m^2. There were no significant differences for any of the aforementioned demographic determinations between the subgroups of neurological deficit within the SCI sample (complete tetraplegia, incomplete tetraplegia, complete paraplegia, incomplete paraplegia). For the total group, subjects with complete tetraplegia had significantly higher plasma glucose values, at 60, 90, and 120 minutes, and plasma insulin levels, at 90 and 120 minutes, than the other three subgroups of neurological deficit, and had a greater frequency of disorders of glucose tolerance (73% vs. 44%, 24% and 31%, respectively; $X^2 = 36.9$, $p < 0.0001$). Males and females had similar serum glucose concentrations, but the plasma insulin levels were significantly higher in the males, at 30, 60, and 90 minutes. By ethnicity, there was no significant difference in the serum glucose or plasma insulin response.

Conclusion: Subjects who were the most neurologically impaired exhibited the worst oral carbohydrate tolerance. Furthermore, for the same BMI, men were more insulin resistant than women were.

Treatment with Calerol and Providine Supplemental Calcium Reduces Serum PTH Levels in Persons with SCI. W. Bauman[1,2] and A. Spungen[1]. [1]Mount Sinai School of Medicine, New York, NY, and [2]Bronx VA Medical Center, Bronx, NY.

Spinal cord injury (SCI) results in disuse osteoporosis. Further loss of bone secondary to readily reversible metabolic conditions should be avoided. Persons with SCI are at an increased risk of being vitamin D deficient (Bauman, Metabolism 1995) due to several predisposing factors, including avoidance of milk, reduced sunlight exposure, and medications that accelerate hepatic metabolism. In a prior study, daily intake of vitamin D (800 IU) for two weeks failed to significantly change the vitamin D level (unpublished observation).

Aims: To study the effect of 2 weeks of therapy with 25 hydroxyvitamin D [25(OH)D; Calderol 50 g BIW] and calcium supplementation (1.5 g elemental calcium/day) in 10 subjects with vitamin D deficiency (i.e., levels less than 16 ng/mL).

Methods: Serum was drawn for 25(OH)D and intact immunoreactive parathyroid hormone (iPTH) (Nichols Institute) at baseline and on days 1 and 14 of therapy.

Results: The results are expressed as mean ± SD. The mean age of the subjects was 53 ± 15 years and the duration of injury, 27 ± 14 years. From baseline to day 14, the mean serum calcium concentration increased from 8.9 ± 0.4 to 9.2 ± 0.5 mg/dL, n.s., and the urinary calcium excretion increased from 103 ± 81 to 184 ± 145 mg/24 hr, $p < 0.01$. The mean serum 25(OH)D levels increased on therapy: 8.7 ± 2.1 to 12.5 ± 3.3 to 14.7 ± 3.6 ng/mL, $p < 0.0005$. However, the therapy prescribed was insufficient to raise the vitamin D levels into the normal range in 8 of 10 subjects. Of note, mean serum iPTH levels decreased while on therapy: 35 ± 26 to 23 ± 14 to 17 ± 12 pg/mL, $p < 0.01$.

Conclusion: In persons with SCI, replacement of 25(OH)D and supplementation with oral calcium will reduce the secondary increase in iPTH levels, which may be expected to decrease skeletal turnover and bone loss in a skeleton already regionally osteoporotic.

Analysis of the BTK Gene on Chromosome X as a Candidate Gene in Graves' Disease. R. Villanueva[1], Y. Tomer[1], S. Tucci[1], D.A. Greenberg[2], E.S. Concepcion[1], and T.F. Davies[1]. [1]Division of Endocrinology and Metabolism, Department of Medicine, and [2]Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

Graves' disease (GD) develops as a result of genetic susceptibility and environmental triggers. The disproportionately higher prevalence in women suggests mechanisms related to pregnancy or susceptibility genes on the X-chromosome. Since women have two X chromosomes, they are twice as likely to inherit an X-chromosome susceptibility gene. We recently screened the X-chromosome using a set of polymorphic microsatellite markers. In the region Xq21.33-22, we found a locus — DXS8020 (designated GD-3) — which was linked to GD with a maximum LOD score (MLS) of 2.5. Among the genes mapped to this region is the Bruton's tyrosine kinase (BTK) gene which encodes for a tyrosine kinase protein important in B cell ontogeny. Inactivating mutations of the BTK gene cause X-linked agammaglobulinemia.. It is also possible that mutations of BTK may influence susceptibility to autoimmunity. Indeed, the mouse gene homologous to BTK (xid) has been shown to modulate the expression of collagen autoimmunity in susceptible mouse strains. Therefore, we investigated the BTK gene as a candidate susceptibility gene for GD. We performed an association study comparing the frequencies of two single stranded conformation polymorphism (SSCP) alleles of the BTK gene resulting from a single base polymorphism (C or A) at position 2228. Seventy (70) Caucasian patients with GD (60 females and 10 males) and 67 healthy Caucasian controls (57 females and 10 males) were studied. The region containing the C/A polymorphism was amplified using P-32-labeled alpha-dCTP. The fragments were separated by polyacrylamide gel electrophoresis (PAGE) according to standard protocols. Twenty-four percent (24%) of the samples were analyzed by direct sequencing using an ABI 310 to confirm findings on the SSCP assays. In all cases complete concordance was obtained between the SSCP analysis and the direct sequencing results. Forty-eight percent (48%) of the patients and 49% of the controls had the C allele demonstrating no association between the BTK SSCP alleles and GD ($p = 0.89$). We conclude that the BTK gene is unlikely to be the GD susceptibility gene on Xq21.33-22.

Relationship Between the Appearance of a Novel Prostacyclin Receptor Antibody and Duration of Spinal Cord Injury. N. Kahn, Z. Jingbo, A. Sinha, and W. Bauman. [1]Mount Sinai School of Medicine, NY; and [2]Bronx VA Medical Center, Bronx, NY.

Coronary artery disease (CAD) is accelerated in subjects with chronic spinal cord injury (SCI). We have shown a novel circulating IgG in SCI that specifically blocks the high-affinity PGI_2 receptors on the platelet surface without affecting the low-affinity PGI_2 receptors.

Aims: In this study we determined the time required to develop measurable amounts of the IgG to the high-affinity prostacyclin receptor as a function of duration of SCI.

Methods: Blood samples were collected 1, 3, 5, 10 and >10 (15 ± 4) years after SCI ($n = 36$). Plasma samples (50 g) were analyzed by polyacrylamide gel electrophoresis (PAGE) followed by densitometery.

Results: The optical density (OD) of the IgG (47,000 K) at 1 year was 1.65 ± 0.08 versus the controls; 1.33 ± 0.04 ($p < 0.01$). A progressive increase of antibody levels for the first 5 years after injury was observed in both paraplegia ($n = 25$) and quadriplegia ($n = 11$). The level of antibody appeared to plateau after 5 years of SCI; after 5, 6–10 years and >10 years of injury the OD's were 1.85 ± 0.12, 1.82 ± 0.13 and 1.84 ± 0.15, respectively. The increase of IgG was directly related to the decrease of binding of prostacyclin to its high-affinity receptors in SCI platelets. Scatchard analysis of ^{3}H-PGE$_1$ binding showed a significant loss of high-affinity receptor numbers ($n_1 = 43 \pm 12$ vs. $n_1 = 172 \pm 25$ sites/platelet, $p < 0.001$) with no significant change in receptor affinity ($kd_1 = 6.1 \pm 2.15$ vs. $kd_1 = 8.1 \pm 2.7$ nM). The level of the high-affinity PGI_2 receptor antibody observed in individuals with SCI was directly associated with the duration of injury, not the level of injury.

Conclusion: An early, aggressive approach aimed at preventing elevations in high-affinity PGI_2 receptor IgG may be advantageous in reducing the progression of vascular diseases in SCI subjects and hence the atherogenic potential of the SCI platelets.

Synaptophysin Immunoreactive Contacts onto GnRH Cells in Hypogonadal Mice Grafted with Normal Preoptic Area: Correlation to Functional Recovery. G. Rajendren and M.J. Gibson. Division of Endocrinology, Mount Sinai School of Medicine, New York, NY.

The integration of gonadotrophin-releasing hormone (GnRH) neurons grafted into the third cerebral ventricle (3V) of hypogonadal (HPG) female mice was investigated. HPG females grafted in the 3V with preoptic area

(POA) obtained from normal fetal mice were assessed for gonadal development. HPG/POA mice with signs of gonadal development ($n = 4$) or those without any noticeable gonadal activation ($n = 4$) were primed with estrogen and progesterone and were paired with sexually active males. Two hours after the mating tests, the brains were fixed and were processed for triple immunohistochemical staining for Fos, GnRH, and synaptophysin. Fos immunoreactivity was observed in the GnRH cells in 3 out of 4 HPG/POA mice with gonadal development, whereas GnRH cells in the non-responders did not exhibit Fos in their nuclei. The number of synaptophysin immunoreactive contacts onto GnRH cells in HPG/POA mice with gonadal development was 6.47 ± 1.05 (mean ± sem) vs. 3.53 ± 0.56 in HPG/POA mice showing no signs of activation of the reproductive axis. The difference was statistically significant ($p < 0.05$). The results suggest that activation of reproductive functions in HPG/POA mice may be dependent on synaptic inputs to the transplanted GnRH cells.

The Effect of Anabolic Steroid Therapy on Healing of Long-Standing Pressure Ulcers: Case Reports of Nine Individuals with SCI. A. Spungen[1], M. Rasul[2], K. Koehler[2], A. Cytryn[2], and W. Bauman[1,2]. [1]Mount Sinai School of Medicine, New York, NY; and [2]Bronx VA Medical Center, Bronx, NY.

Non-healing pressure ulcers are a frequent and debilitating problem for individuals with spinal cord injury (SCI). Anabolic steroid therapy combined with increased protein intake has been successful in promoting weight gain, reversing catabolism and increasing the rate of skin closure from burns.

Aims: To evaluate the effect of oxandrolone 20 mg/day and glutamine 20 g/day use in the treatment and healing time of non-healing stage III pressure ulcers (4x4 cm in surface area) in nine individuals with SCI.

Methods: Nine patients were selected based on having at least one of the following two criteria: severity of the wound (full thickness through fascia into muscle, tendon and/or bone) and duration of non-healing status (self-reported or hospitalized documentation of no change or worsening status of greater than 2 months). Patients were administered: oxandrolone 20 mg/day (BTG Corp, Iselin, NJ) and glutamine 20 g/day dissolved in applesauce or juice (Cambridge Nutraceuticals, Boston, MA). Liver function tests and lipid profile analyses were performed by routine methods in the Bronx VA Medical Center Clinical Chemistry Laboratory.

Results: After treatment with oxandrolone and glutamine: two subjects healed in 12 months, one healed in 6 months, two healed in 4 months, three healed in 3 months, and one patient's progress was unknown due to a self-requested discharge from the hospital. Mild elevation in liver function tests (ALT and AST) was observed.

Conclusion: Prior attempts to promote wound healing by topical pharmacological interventions have had marginal effects. Although clinical case studies have limited usefulness for determining a drug effect, these initial observations have been promising. Our group has planned a double-blind placebo trial to test the efficacy of treatment with oxandrolone in individuals with SCI and non-healing pressure ulcers.

New Insights into the Genetic Susceptibility to Autoimmune Thyroid Diseases. Y. Tomer[1], G. Barbesino[1], D.A. Greenberg[2], E Concepcion[1], and T.F. Davies[1]. [1]Division of Endocrinology and Metabolism, Department of Medicine and [2]Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

The autoimmune thyroid diseases (AITDs) include two related disorders, Graves' disease (GD) and Hashimoto's thyroiditis (HT), in which perturbations of immune regulation result in immune reaction to the thyroid gland. In Graves' disease, the autoimmune process results in the production of thyroid-stimulating antibodies and leads to hyperthyroidism, while in Hashimoto's thyroiditis the end result is destruction of thyroid cells and hypothyroidism. The AITDs appear to develop as a result of a complex interaction between inherited predisposing genes and environmentally encountered triggering agents. Even though GD and HT have different clinical presentations, it is likely that similar mechanisms lead to the immune attack on the thyroid in both diseases, since they appear in the same families. Thus, it has been postulated that a similar genetic contribution is involved in their development. In order to identify the susceptibility genes for GD and HT, and to examine whether they are unique to each disease or common to both diseases, we performed a whole genome linkage study in patients with AITD. We studied a data set of 56 multiplex, multigenerational AITD families (354 individuals), using highly polymorphic and densely spaced microsatellite markers (inter-marker distance < 10 cM). Linkage analysis was performed using two-point and multipoint parametric methods (classical LOD score analysis). We identified 5 loci which were linked with AITD. Three loci were linked with GD but not with HT and were termed GD-1, GD-2, and GD-3. One locus was linked with HT only in a subgroup of the families (HT-1), and one locus was linked with both GD and HT (AITD-1). We found no linkage to the HLA and CTLA-4 regions which previously were reported to be weakly associated with GD. These results demonstrate that unique and common genes confer susceptibility to GD and HT. It is possible that the wide range of clinical phenotypes of HT caused the lack of identification of more susceptibility loci for HT.

Gastroenterology

Intravenous Conjugated Estrogen for the Control of Recurrent Gastrointestinal Bleeding from Angiodysplasia in a Patient with Chronic Renal Failure (CRF). E.Y. Baghal, N.J. Dababneh, G. Pavlou, and W.J. Baddoura. Division of Gastroenterology, St. Joseph's Hospital and Medical Center, Paterson, NJ; and Seton Hall University School of Graduate Medical Education, South Orange, NJ.

Introduction: Gastrointestinal (GI) bleeding from angiodysplasia associated with chronic renal failure is not uncommon. Management of such cases can be quite challenging and problematic, as demonstrated in the following report.

Case Report: A 52-year-old male with a history of CRF and hypertension presented with a one-week history of tarry stools not associated with pain or diarrhea. The patient had upper and lower endoscopic examinations, including small bowel enteroscopy, which failed to reveal a definite source of bleeding. Angiogram was negative but bleeding scan showed trace uptake of radionuclide in the proximal duodenum. The patient continued to bleed intermittently over a period of approximately three months, during which he received a total of 85 units of packed red blood cells in addition to other blood products for correction of prolonged bleeding time. On subsequent examinations, several bleeding angiodysplastic lesions were identified in the duodenum, and despite endoscopic electrocoagulation therapy, hemostasis could not be achieved. Combined oral estrogen and progesterone therapy also failed to stop bleeding. As a last resort, conjugated estrogen was administered intravenously at a dose of 0.6 mg/kg/day for five consecutive days. The hemogram remained stable with no further bleeding over the next three months, at which time the patient expired of unrelated causes.

Conclusion: Conjugated estrogen given intravenously can be effective in the control of recurrent GI bleeding in patients with chronic renal failure. The exact mechanism of action remains undetermined, though beneficial effect on platelet function has been demonstrated in the past.

The Role of Nitric Oxide in Cerulein Pancreatitis: Studies in iNOS KO Mice. M.A. Korsten[1] and J.J. Ma[2]. [1]Bronx VA Medical Center, Bronx, NY; and [2]Beijing Medical University, Beijing, People's Republic of China.

Microcirculatory alterations appear to play an important role in the pathogenesis of cerulein pancreatitis (CP). Recent studies suggest that these changes in the microcirculation may be mediated by nitric oxide (NO), a potent vasodilating substance. Genetically engineered mice lacking the iNOS (inducible nitric oxide synthase) gene now permit a direct assessment of the importance of NO production in this rodent model of pancreatitis.

Methods: 6–8 week old male mice (C57BL/6 and iNOS KO) were administered cerulein (Sigma) by IP injection (at doses of 0, 10, 30, 60 and 90 g/kg BW) at hourly intervals for 7 hours and sacrificed 24 hours after the last dose. Pancreatic weight (mg/g BW), plasma nitrite (mM), plasma amylase (U/l) and myeloperoxidase activity (MPO) were assessed as measures of pancreatic injury.

Results: In genetically intact C57BL/6 mice ($n = 6$ in each group), we observed a significant (using ANOVA) dose-dependent increase in pancreatic wt. (C0:7.4 ± 0.29; C10:8.2 ± 0.34; C30:8.9 ± 0.51; C60:10.5 ± 0.58; C90:11.1 ± 0.76), plasma nitrite (C0:4.6 ± 0.4; C10:5.2 ± 0.6; C30:6.0 ± 0.7; C90:7.6 ± 0.8) and plasma amylase (C0:63.6 ± 5.4; C10:72.1 ± 6.2; C30:94.3 ± 7.1; C60:126.5 ± 8.4; C90:148.2 ± 9.6) after cerulein. Based on this initial data, a cerulein dose of 60 g/kg was used for studies in which the pancreatic response to cerulein was compared in normal and iNOS KO mice. Pancreatic wt. was greater (12.8 ± 0.74 vs. 10.5 ± 0.58, $p < 0.05$), plasma nitrite was lower (4.5 ± 0.5 vs. 6.8 ± 0.6, $p < 0.05$) and plasma amylase was higher (162.5 ± 9.7 vs. 126.5 ± 8.4, $p < 0.02$) in iNOS KO mice as compared to C57bl/6 mice. Finally, the level of MPO was enhanced in iNOS KO mice (26 ± 2.8 vs. 18 ± 2.4, $p < 0.05$). These differences were attenuated by the administration of isosorbide dinitrate to iNOS KO mice.

Conclusion: NO production plays a protective role in CP, in part, by preventing the accumulation of leukocytes. To the extent that this rat model resembles events in early human pancreatitis, measures that increase NO levels may have clinical value.

Geriatrics

Knowledge and Attitudes of Geriatricians Regarding Dementia Patients Who Drive and Are a Danger to Others on the Road: A National Survey of Geriatricians. S. Gerges, G. Cable, M. Reisner, and V. Thirumavalavan. Mount Sinai School of Medicine, New York, NY; and The Jersey City Medical Center, Jersey City, NJ.

Objectives: To determine geriatricians' attitudes and knowledge about the steps to take with their dementia patients who drive and may be dangerous on the road.

Design: A survey sample of geriatricians in the United States.

Results: Nearly 3 of 10 geriatricians (28.7%; 95% Confidence Interval [CI], 24.3% to 33.1%) do not know what steps to take in their state to report dementia patients who drive and may be a danger to others on the road. Most geriatricians in all states (74.8%; 95% CI, 70.5% to 79.1%) agreed that physicians are responsible for reporting dementia patients who drive and may be a danger to others. Similarly, over 90% (92.7%; 95% CI, 90.1% to 95.3%) of geriatricians said that they would contact the appropriate authority to recommend that patient driving privileges be revoked. Moreover, geriatricians would be willing to recommend revocation over the objections of patients (86.9%; CI, 83.6% to 90.2%), though a smaller percentage would recommend revocation of driving privileges over the objections of the patient's family (74.5%; 95% CI, 70.5% to 78.8%).

Comment: Although large majorities of geriatricians believe they are responsible for reporting dementia patients who drive, and will act to have driving privileges revoked, only a minority of geriatricians know what steps to take to report patients who drive.

Hematology

GPIIb/IIIa-Dependent Platelet-Platelet Interactions Come Before Rather than After Platelet Adhesion and Spreading for Most Platelets Depositing on Collagen under Static Conditions. D. Patel, H. Vaananen, C. Boger, and B.S. Coller. Mount Sinai School of Medicine, New York, NY.

The traditional description of platelet interactions with collagen-coated surfaces is that platelets (P) first adhere and spread to form a monolayer, and then this first layer of P recruits additional layers of P to commence platelet thrombus formation.

Objective: To study this phenomenon of platelet-platelet interactions and the role GP IIb/IIIa has in this process.

Methods: We developed a microchamber allowing concurrent time-lapse recording of 12 separate samples using phase contrast microscopy. The chamber consists of a silicone elastomer-coated glass slide, a silicone elastomer gasket, and a #1.5 coverslip coated with polystyrene. The microscope system consists of an inverted microscope, a 100 X 1.4 N.A. objective, a video camera, and a mechanical stage under computer control. Images were obtained automatically for 2 hrs from each channel at 2.4 min intervals and stored on a video disk recorder. Each acquired image was an average of 2 video frames from the camera. Chambers were coated with purified type 1 lathyritic rat skin collagen at 33 g/mL in 0.05% HAc, blocked with 0.5% BSA, and washed with modified Tyrode's buffer (MT) containing Mg^{++}. Human P were prepared from ACD blood either by gel filtration in Tris-saline (T-S), pH 7.4, or by combining PRP with platelet-rich buffer obtained from buffy coats using MT. P in MT or T-S with Mg^{++} were added to the chambers, either with or without pretreatment with mAb 7E3 (anti-GPIIb/IIIa + v3) at 10 g/mL for 15 min at 22°C.

Results: The results with untreated P differed from the traditional description, in that soon after the initial adhesion of relatively few P, additional P appeared to be recruited via their filopodia to the adherent P, and then the recruited P went on to: (1) adhere and spread nearby, (2) continue to interact laterally and vertically with the recruiting platelet, and in some cases (3) recruit additional P that then went on to adhere and spread. In the presence of mAb 7E3, platelet-to-platelet recruitment was nearly eliminated, but a monolayer formed nonetheless by direct adhesion to collagen, although with little evidence of lateral or vertical cohesion between P.

Conclusion: These data indicate that, at least under static conditions, platelet adhesion, spreading and recruitment on collagen are not rigidly sequential processes, but rather concerted processes; moreover, although GPIIb/IIIa is not required for P to deposit on collagen, the deposition process is fundamentally different in the absence of functional GPIIb/IIIa receptors.

The AML/ETO Fusion Protein Modulates the Transcriptional Effects of Histone Deacetylases, PLZF and Other Correpressor Proteins. A. Melnick[1], J.J. Westendorf[1], S. Arai[1], B. Lutterbach[1], H.J. Ball[1], A. Polinger[1], S.W. Hiebert[2], and J.D. Licht[1]. [1]Mount Sinai School of Medicine, New York, NY; and [2]Vanderbilt University School of Medicine, Nashville, TN.

The promyelocytic leukemia zinc finger (PLZF) protein is a transcriptional factor disrupted in a subset of patients with acute promyelocytic leukemia (APL). PLZF has been demonstrated to interact with a transcriptional repression complex which includes the nuclear receptor co-repressors N-CoR and SMRT, Sin3-A and histone deacetylases (HDACs). ETO, involved in the (8; 21) AML–M2 translocation, also associates with the same transcriptional repression complex. These commonalities led us to ask whether ETO and PLZF associate together, and if this interaction has functional significance. Using the yeast-two-hybrid system and mammalian cell co-immunoprecipitation assays and immunofluorescence assays, we demonstrated for the first time that these two proteins do interact. This occurred both for overexpressed and endogenous proteins. Furthermore, we found that ETO is able to enhance the ability of PLZF to repress transcription. This effect was further increased when co-repressors and HDACs were titrated into these reactions. The interaction was mapped to the N-terminal region of ETO and is not dependent on the PLZF POZ/BTB repression domain. We conclude that ETO is a co-repressor for PLZF repression, by virtue of its ability to recruit a transcriptional repression complex which depends at least in part on HDAC chromatin condensation. This is further supported by the fact that HDAC inhibitors abrogated the combined transcriptional repression of PLZF and ETO. We then wished to know if the AML/ETO fusion protein, product of the t(8;21) translocation, could disrupt ETO and PLZF functions. We found that: (1) AML/ETO is able to partially antagonize transcriptional repression mediated by PLZF; (2) AML/ETO completely abrogates the cooperative effect of PLZF and ETO; (3) AML/ETO is able to block the transcriptional cooperation between PLZF and other co-repressors such as N-CoR and SMRT; (4) AML/ETO is able to antagonize transcriptional repression mediated by HDACs 1, 2 and 3; and (5) AML/ETO can antagonize the transcriptional repression mediated by the aberrant PLZF/RAR fusion partner on its binding sites. Thus, we conclude that AML/ETO behaves as a dominant negative factor, not only for ETO but for other myeloid specific transcriptional regulators. This dysregulation suggests a common pathway of leukemogenesis in several myeloid leukemias.

The HMG Domain Protein SSRP1 is a Cofactor in Transcriptional Activation. P.J. Hayes, D. Dias, M.A. Dyer, and M.H. Baron. Divisions of Hematology and Medical Oncology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Globin gene switching in humans is a process in which embryonic, fetal, or adult globin genes are sequentially activated and then silenced in erythroid cells at distinct stages of development. We have focused on the earliest-expressed human b-like globin gene, e, and have previously shown that activation of the gene requires the cooperation of a collection of positive and negative regulatory elements termed PREs and NREs, respectively. PRE II synergizes with at least two other elements, PRE V and PRE I, to activate a minimal promoter. Its activity requires the binding of a nuclear factor of ~85–90 kDa, termed PREIIBF, that specifically interacts with a novel 19 bp region within PRE II. Nuclear extracts prepared from adult erythroid cells contain a PRE II binding activity that exhibits faster mobility in electrophoretic mobility shift assays. A number of biochemical and molecular criteria suggest that embryonic and adult forms of the two proteins are very similar. The distinct forms of PREIIBF are expressed from a single gene, do not appear to be translated from alternatively spliced transcripts, but may result from differential post-translational modifications such as phosphorylation, proteolysis, and/or glycosylation. PREIIBF was extensively purified from a human erythroid cell line and shown to introduce a bend into its target PRE II site. We have previously proposed that PREIIBF acts as an architectural transcription factor to bring together distantly bound proteins upstream of the human e-globin gene in a process that might involve DNA bending and/or looping. cDNA expression cloning followed by biochemical and immunological characterization revealed that PREIIBF is the HMG domain SSRP1. We have shown that SSRP1/PREIIBF lacks a classical activation domain. Therefore, at least in the context of non-erythroid cells, SSRP1/PREIIBF does not function as a classical activator. Yet, the amino-terminal two-thirds of the protein is very highly conserved from yeast to humans. On the hypothesis that one function of this domain may be to interact with and recruit other proteins to the DNA, we have isolated several potential SSRP1 partners in erythroid cells using a yeast two-hybrid screen. Recently we have shown that SSRP1 stimulates both DNA binding and transcriptional activation by the Serum Response Factor (SRF) transcription factor (Spencer, MHB and Olson, 1999 JBC 274:15686). It seems likely that SSRP1/PREIIBF functions at least in part through interactions with other proteins, perhaps through recruitment of proteins that contain activation domains (which might function in an erythroid-specific manner) or by promoting higher-order assemblies of proteins, thereby promoting interactions with the basic transcriptional machinery.

***Development of a Murine Endothelial Cell Line with Multilineage Potential Derived from Adult Murine Bone Marrow.** I.S. Meeus, R.S. Weinberg, and G.F. Atweh. Division of Hematology, Mount Sinai School of Medicine, New York, NY.

In the course of performing gene transfer experiments, we observed the development of an unusual lymphoproliferative disease in a set of 5 W/W^v mice. These mice were previously transplanted with C57BL/6J bone marrow that was plated *ex vivo* in Dexter-type, long-term bone marrow culture and transduced with an ecotropic murine moloney leukemia retroviral construct carrying the human-globin gene. The disease first manifested 4 months after transplantation as massive hepatosplenomegaly with severe itching. One of the 5 mice died spontaneously and was found to have a malignant lymphoma (with features of plasmacytoid differentiation) that infiltrated the liver and spleen. The other four animals were sacrificed as they became moribund, and their bone marrows were harvested. Bone marrow cells from these mice were plated *in vitro* in the presence of erythropoietin and developed into a factor-independent cell line (DC2) that had striking endothelial characteristics. The cell line grew in culture as a mixture of adherent and non-adherent cells. The non-adherent cells showed morphological features typical of plasma cells. The attached cells had a tendency to line up in long highway-like structures that extended from one end of the tissue culture plate to another. When the DC2 cells were plated in Matrigel® (a semisolid medium rich in extracellular matrix proteins), they gave rise to branching tubular structures that resembled blood vessels. When the cells were maintained in culture until they reached confluence and arrested their growth, some cells in the adherent layer accumulated cytoplasmic lipid-rich vacuoles typical of adipocytes. The same spectrum of morphological features was seen in multiple clonal cell lines that were isolated from the primary cell line by limiting dilution. Cell surface phenotypic analysis showed positive staining for Flk-1, also known as murine VEGF-2 receptor, (endothelial marker), Tie-2 (endothelial marker), CD34 (endothelial/hematopoietic marker) and CD31 (endothelial marker). The cells were also positive by flow cytometry for the myeloid marker CD45 (5.7%), CD34 (84%), the endothelial/megakaryocytic marker CD61 (15%), the hematopoietic marker CD38 (7%) and the B-cell marker B220 (3.3%). We believe that the bone marrow cell that gave rise to this established cell line represents a primitive cell capable of differentiation along several distinct lineages that include endothelial, lymphoid, myeloid and adipocytic lineages. The potential for this cell line to contribute to vasculogenesis and hematopoiesis *in vivo* is currently being tested. This cell line may provide unique opportunities to clarify the developmental lineage of the different cell types that constitute the adult bone marrow. It may also serve as a valuable tool in the investigation of the molecular events that underlie lineage commitment and differentiation of endothelial and hematopoietic cells.

Binding of Complement Component C1q to β_2GPI Antibodies from Patients with Antiphospholipid Syndrome. M. Odorczuk, L.B. Keil, and V.A. DeBari. Laboratory of Experimental Medicine, Department of Medicine, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Antibodies to β_2GPI and other phospholipid-binding proteins are associated with and may contribute to the pathogenesis of antiphospholipid syndrome (APS). Several mechanisms have been proposed whereby the ${}_2$GPI –anti-β_2GPI reaction would lead to the thrombotic state characteristic of APS. We are interested in exploring whether complement activation by these complexes contributes to the physiology of APS.

Objective: To determine if anti-β_2GPI reactive with surface-bound β_2GPI can bind C1q, i.e., to determine whether surface-bound β_2GPI –anti-β_2GPI immune complexes can initiate the classical pathway of complement activation.

Methods: β_2GPI was bound to chemically activated microtiter plates which had previously been shown to promote anti-β_2GPI reactivity with bound β_2GPI. Wells with surface-bound β_2GPI (capped with bovine serum albumen) were then reacted with complement-inactivated (C_{in}) sera from patients (pts) or with C_{in} control sera. Following removal of unbound serum components, the wells were incubated with biotinylated C1q and probed with peroxidase-conjugated streptavidin. Bound C1q was detected at 450 nm using tetramethyl benzidine/peroxidase as a substrate system and expressed as Absorbance units (Abs).

Results: We identified 17 pts with elevated anti-β_2GPI: 4 pts with IgG only, 4 with IgM only, 1 with IgA only, 1 with IgG and IgA, 6 with IgG and IgM, and 1 with IgG, IgA and IgM. C1q binding from 15 normal controls (con) was 0.05 ± 0.03 (SD). Of the APS pts, 13/17 (76%) had Abs > 5 SD above con. The 4 pts with C1q Abs within normal limits had, respectively, IgM only (2), IgA only (1), and both IgG and IgM (1). Statistical analyses (ANOVA followed by Neuman-Keuls) suggest differences IgG and IgG + IgM groups compared to con (ANOVA: $p < 0.0001$; Neuman-Keuls: con vs. IgG, $p < 0.05$; con vs. IgG + IgM, $p < 0.001$.

Conclusions: Anti-β_2GPI from APS appear to have a variable degree of C1q affinity. Although this is most likely a function of anti-β_2GPI Ig isotype and titer, those patients with strong C1q binding responses are likely to have an inflammatory component to their disease processes.

Properties of the Hololipoprotein Complex Formed from $\beta_2$glycoprotein I and Dicaproyl Phosphatidylserine. J.D. Kohles[1,2], M. Petersheim[2], and V.A. DeBari[1]. [1]Laboratory of Experimental Medicine, Department of Medicine, St. Joseph's Hospital and Medical Center, Paterson, NJ; and [2]Department of Chemistry, Seton Hall University, South Orange, NJ.

Several phospholipid (PL) binding proteins have been implicated as the targets for autoantibodies from patients with antiphospholipid syndrome (APS) including $\beta_2$glycoprotein 1 (β_2GPI), a 54 kDa glycoprotein consisting of five "sushi" domains. Within the fifth domain is a region from cys 281-cys 288 which contains 4 lys residues which can bind anionic PL.

Objective: To clarify the role of the lipid-binding site in the presentation of the autoepitope of β_2GPI by generating a hololipoprotein in solution, thus segregating the surface-binding requirement from the chemical alteration of the apoprotein by lipid.

Experimental Approach: We describe our studies of the holopoprotein generated by reacting β_2GPI with dicaproyl phosphatidylserine (DCPS).

Results: The formation of the β_2GPI-DCPS complex is accompanied by inhibition of β_2GPI binding to PL-coated (dimyristoyl phosphatidic acid, 80%/dimyristoyl phosphatidyl choline, 20%) polystyrene surfaces (fit to sigmoidal dose response model was: $r^2 = 0.995$). DCPS at concentration > 10 mM also displaces β_2GPI bound to anionic PL surface. When the β_2GPI-DCPS complex bound to untreated polystyrene was probed with human APS autoantibodies, a slight increase in apparent binding was observed with maximum activity at a ratio of DCPS/β_2GPI of $7.2x10^4$. However, the apparent binding observed in this system was only 22% of that shown by β_2GPI-anti-β_2GPI on activated polystyrene.

Conclusions: These data demonstrate that, although binding of a low molecular weight anionic PL to β_2GPI might minimally enhance binding of autoantibodies from APS serum, the extent of this binding does not compare favorably to that observed when β_2GPI is bound to a surface with characteristics which elicit optimal autoepitope exposure. This suggests that lipid binding itself is not a sufficient condition for the generation of the autoepitope.

A Pre-Clinical Study of the Stability of Reconstituted Urokinase Solutions. H. Asa'd[1], J.D. Kohles[1], J.R. Sterrett[2], M. Weld[3], P. Gunning[3], and V.A. DeBari[1]. [1]Laboratory of Experimental Medicine and [2]Division of Nephrology, Department of Medicine, and [3]Pharmacy Department, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Urokinase, a plasminogen activator (PA) from cultured kidney cells, has been used extensively in clinical situations requiring clot lysis. The stability of reconstituted urokinase solutions is an issue of considerable importance to health care facilities, especially tertiary-level medical centers, because of the potential cost savings derived from the use of stored aliquots of this enzyme.

Objective: To investigate the in vitro activity of urokinase over a two-month period at temperatures (C ± range) of -70 ± 4, -20 ± 2, 7 ± 1 and 37 ± 1.

Methods: Urokinase was reconstituted with normal saline and stored in polypropylene syringes with polyisophene plunger tips. Aliquots were assayed for PA activity by the Sigma method using casein as a substrate for proteolysis. Immediately after t0 (initial time) assay, aliquots were stored at the temperatures indicated. At intervals up to 56 days, specimens were withdrawn and assayed.

Results: Over the period from t_0 to 56 days, no significant decrease in activity was observed; slopes indicated a % activity/day = –0.18 ± 0.27, –0.08 ± 0.22, 0.05 ± 0.21 and –0.20 ± 0.26, for aliquots maintained at -70EC, –20°C, 7°C and 37°C, respectively. Neither slopes nor intercepts varied significantly as assessed by ANOVA (p = n.s.). Studies of urokinase activity at 60°C demonstrated 21% decrease in activity after 3 hr. An aliquot heated to 100°C for 30 min demonstrated obvious denaturation; a suspension of this specimen showed no activity.

Conclusion: These data strongly suggest that thrombolysis with urokinase solutions stored for extended periods should be possible and should be examined in an *in vivo* clinical trial.

Anti-phospholipid Antibody Syndrome: A Case Report with Critical Review. L.M. Sheldon, S. Grossman, and A.D. Rubin. Department of Medicine, St. Joseph's Hospital and Medical Center, Paterson, NJ.

We report a case of Anti-phospholipid Antibody Syndrome (APS) in an adult male, with thrombocytopenia, followed by a review of the literature on APS.

Case Report: A 63-year-old male with a past medical history of diverticulitis, peptic ulcer disease, and recent coronary artery bypass surgery was readmitted for treatment of psychosis and depression after he presented confused and complaining of depression and insomnia. He had no previous personal or family history of hypertension, diabetes, autoimmune diseases, or thrombotic tendencies. His previous hospitalization was complicated only by a mild thrombocytopenia, and his medications were Lopressor, Ecotrin, Pepcid, and Pravachol. On re-admission, his vital signs were stable and his physical exam unremarkable. Lab results showed platelets of 78,000/μL, PT of 13.9, PTT of 54.1 and an INR of 1.2. There were no new EKG changes. A computed tomography (CT) scan of the head was negative. Over the next few days, renal function deteriorated, with BUN and creatinine climbing to 38/3.3. Laboratory tests were negative for ANA and RF, but anti-cardiolipid antibodies were positive. ESR was 82. Administration of high dose corticosteroids resulted in normalization of renal function within two days. However, patient's thrombocytopenia worsened, with platelets falling to a low of 13,000/μL. Platelet transfusions, intravenous immunoglobulin, and steroids had a limited and transient effect on his platelet counts. On day 17, the patient developed focal weakness and the diagnostic workup revealed a CVA. Warfarin anticoagulation was considered and rejected because of the patient's bleeding history and refractory thrombocytopenia. To raise his platelet count, a course of plasmapheresis with fresh frozen plasma was begun. His platelet count rebounded, with increased counts showing a strong temporal association with plasmapheresis sessions. After three months, platelet counts were sustained at or above 30,000; the patient no longer required plasmapheresis and had experienced no further thrombotic episodes.

Antiphospholipid syndrome is characterized by recurrent venous or arterial thromboses, spontaneous abortion, and/or thrombocytopenia accompanied by positive antiphospholipid antibody titers. Approximately 25% of APS patients have thrombocytopenia and are at risk for both thrombosis and bleeding at very low platelet counts. The pathogenesis of APS is not fully understood and is an area of active research. Potential mechanisms may involve antibody interaction with 2GPI, the Protein C pathway, eicosanoids, and endothelial cells. Warfarin is the recommended treatment for thromboses, and corticosteroids are the drugs of choice to raise platelet counts prior to the introduction of warfarin.

Induction of Hematopoiesis and Vasculogenesis by Diffusible, Nonmesodermal Signals and Potential Stem Cell Targets in the Developing Mouse Embryo. M.H. Baron[1,2], M.A. Dyer[1], M. Minou[1], H. Snoeck[2], and J. Zavadil[1]. [1]Divisions of Hematology and Medical Oncology, Department of Medicine, and [2]Institute for Gene Therapy and Molecular Medicine, Mount Sinai School of Medicine, New York, NY.

Blood formation and vasculogenesis in the yolk sac of the mammalian embryo are processes that begin during gastrulation and first require the induction of mesoderm during gastrulation. The first blood and vascular endothelial cells form when the extraembryonic mesoderm is induced to differentiate. However, little is known about the molecules involved in these processes during embryonic development. To examine the possibility that epithelial-mesenchymal interactions play an important role in yolk sac hematopoiesis and vasculogenesis in the mouse, we devised a novel transgenic embryo explant culture system. Transgenic embryos harvested prior to the formation of blood (i.e., before or early in gastrulation) are stripped of their surrounding primitive endoderm (epithelium) and grown in collagen drop cultures alone or together with the isolated endoderm tissue. Using this system we have demonstrated that primitive (visceral) endoderm signaling is essential for activation of primitive hematopoiesis and embryonic vasculogenesis. The signals mediating these epithelial-mesenchymal interactions are short-range, diffusible and stage-dependent, becoming less potent around late gastrulation and eventually undetectable. Remarkably, primitive endoderm signaling can respecify (reprogram) hematopoiesis and vasculogenesis in tissue that is not fated to form blood or vascular cells. For example, anterior embryonic ectoderm (prospective neurectoderm) can be respecified along hematopoietic and vascular lineages when cultured with visceral endoderm tissue. We are currently pursuing two major lines of experimentation: the identification of the endodermal signaling molecules, and the characterization of stem cells that arise during gastrulation. To simplify the assay for testing of recombinant signaling proteins, we have generated transgenic mice in which a green fluorescent protein (GFP) reporter gene is expressed only in embryonic blood cells. Cultured gastrulating embryos activate expression of the GFP gene as mesoderm and then erythroblasts are produced, resulting in green fluorescence that can be detected under UV light. To identify possible target cells of endodermal signaling, we have begun to carry out cell sorting by flow cytometry. We find a surprisingly large population of cells that are Sca1+lin- (a characteristic of adult and fetal stem cells), and the Sca1+ population also expresses both CD34 and c-kit. We are beginning to analyze the developmental potential of these populations using *in vitro* progenitor /stem cell assays.

Endothelial Selectins and VCAM-1 Promote Hematopoietic Progenitor Homing to Bone Marrow. P.S. Frenette[1] and D.D. Wagner[2]. [1]Division of Hematology, Department of Medicine, Mount Sinai School of Medicine, New York, NY; and [2]Department of Pathology, Harvard Medical School, Boston, MA.

The adhesive mechanisms allowing hematopoietic progenitor cells (HPC) homing to the bone marrow after bone marrow transplantation are poorly understood. We investigated the role of endothelial selectins and VCAM-1 in this process. Lethally irradiated recipient mice deficient in both P- and E-selectins (P/E-/-), reconstituted with minimal numbers (5 x 10^4) of wild-type bone marrow (BM) cells, survived the procedure poorly compared to wild-type recipients. Excess mortality in P/E-/- mice, after a lethal dose of irradiation, was likely due to a defect of HPC homing. Indeed, we observed that the recruitment of HPC to the BM was reduced in P/E-/- animals, either splenectomized or spleen-intact. Homing into the BM of P/E-/- recipient mice was further compromised when a function-blocking VCAM-1 antibody was administered. Circulating HPC, 14 hours after transplantation, were greatly increased in P/E-/- mice treated with anti-VCAM-1 compared with P/E-/- mice treated with just IgG or wild-type mice treated with either anti-VCAM-1 or IgG. Our results indicate that endothelial selectins play an important role in HPC homing to the bone marrow. Optimal recruitment of HPC after lethal doses of irradiation requires the combined action of both selectins and VCAM-1 expressed on endothelium of the bone marrow.

G-CSF Primed Bone Marrow Improves Delayed Engraftment Produced by MTX Containing GvHD Prophylaxis Regimens. L. Isola, E. Scigliano, D. Skerrett, and S. Fruchtman. BMT Service, Division of Hematology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Administration of G-CSF leads to increased number of progenitors in harvested bone marrow. We previously demonstrated that G-CSF primed bone marrow (pBM) is a suitable source of stem cells for allogeneic transplantation. Combinations of methotrexate (MTX) with cyclosporin A (CSA) or tacrolimus (FK) are commonly used for graft versus host disease (GvHD) prophylaxis after allogeneic transplantation. Prednisone and CSA or FK regimen results in more rapid hematopoietic reconstitution, but steroids have undesirable side effects.

Aims: We examined whether the use of pBM can offset the delayed engraftment seen with MTX containing GvHD prophylaxis.

Methods: Seventeen (17) patients received pBM from matched sibling donors who received G-CSF at 10 mcg/kg/day for 2–4 days prior to harvesting. Conditioning was total body irradiation/cyclophosphamide (CY), busulfan/CY or total lymphoid irradiation/CY/ATG. All grafts contained 3.5–4 x 10^8 MNC/kg. Ten out of 17 patients received MTX as part of their GvHD prophylaxis. IBMTR definitions of ANC > 500 and plts > 20,000 were used. Historical controls for engraftment were 112 consecutive pts who received allogeneic bone marrow transplant (BMT) at our institution with unstimulated BM (BM). For length of stay, controls were the subset transplanted during 1996.

Results: Neutrophil and platelet engraftment occurred more rapidly in both groups of patients receiving pBM as compared to controls, and this shortened hospitalization (see table). Peritransplant mortality was 18% (3/17). Fourteen patients remain alive on day 57–1014 post-BMT. One patient in the pBM group who received CSA/PRD has extensive chronic GvHD. One who received MTX/CSA had an isolated central nervous system leukemic relapse and is now in complete remission.

Graft/MTX	ANC > 500*	ANC > 1,000*	Plt > 20,000*	Hospital Stay*
BM/yes	24 ± 12	26 ± 13	26 ± 19	46 ± 15
pBM/yes	18 ± 3	21 ± 6	21 ± 6	34 ± 8
pBM/no	14 ± 4	17 ± 3	17 ± 3	36 ± 10

*Mean ± SD

Conclusion: The use of primed bone marrow allografts resulted in more rapid engraftment and shorter hospitalization in this group of patients. Bone marrow priming can partially offset the delay in neutrophil and platelet recovery seen with the use of MTX containing GvHD prophylaxis. G-CSF pBM transplants did not result in higher than expected GvHD, disease relapse and/or peritransplant mortality.

Proteasome-Mediated Degradation of Integrin Receptor Subunits. D.L. French and J.C. Unkeless. Department of Medicine and Immunobiology Center, Mount Sinai School of Medicine, New York, NY.

Integrins are a family of adhesion receptors that mediate cell-cell and cell-extracellular matrix interactions, in both normal and pathologic situations. These interactions are essential for cell survival and are required for functions that include cell adhesion, spreading, migration, and proliferation. Integrin receptors are synthesized in the endoplasmic reticulum (ER) as two single-chain precursor molecules that associate to form a complex that is transported to the cell surface. Subunits may be synthesized at different rates and in different stoichiometric amounts. Mechanisms must be available both for the assembly and transport of stable complexes, and for the orderly degradation of unassembled subunits in the ER. To study the mechanisms of ER-mediated retention and degradation of integrin subunits, we are using transfected CHO cell lines expressing normal and mutant integrin subunits of the prototype integrin receptor, platelet GPIIb/IIIa (IIb 3). This receptor plays a critical role in both hemostasis and thrombosis, and the absence of the platelet integrin GPIIb-IIIa receptor manifests in the bleeding disorder Glanzmann's thrombasthenia. In preliminary studies, a panel of cell-permeable protease inhibitors, including MG132 (10 M) which inhibits the chymotrypsin-like activity of the proteasome, calpains, and cysteine proteases; lactacystin (10 M) which specifically inhibits the chymotrypsin-like activity of the proteasome; NH_4Cl (50 mM) which inhibits lysosomal proteases; and E64d (10 M) which inhibits cysteine proteases, were tested. The results suggested that degradation of GPIIb/IIIa is mediated solely by the proteasome. In addition, the accumulation of normal and mutant integrin subunits expressed in three cell lines incubated in the presence of MG132 showed an ~1.3-fold increase in the amount of a normal GPIIIa subunit, an ~11-fold increase in the amount of a mutant GPIIIaC374Y subunit, and an ~2-fold increase in the amount of another mutant GPIIIaC374-386A subunit. These findings extend our original observations and provide evidence that the proteasome is not only involved in degradation of mutant integrin subunits, but is also involved in degradation of normal integrin subunits. To dissect the effect of inhibitors and chaperone binding proteins on integrin biosynthesis and degradation, an *in vitro* transcription/translation system has been established. This system will complement the *in vivo* system and provide a mechanism to decipher the complexities of ER-mediated retention and degradation of integrin subunits.

Immunobiology

STAT 1 and STAT 3 Activation by a Novel B Cell Differentiation Factor. T. Kraus, C. Horvath, and L. Mayer. Immunobiology Center, Mount Sinai School of Medicine, New York, NY.

We have previously described a novel B cell differentiation factor, termed 446-BCDF, that is secreted by anti-CD3-stimulated T cells. This factor results in a 3–10-fold increase in secreted immunoglobulin (Ig) from SAC-activated B cells and cannot be neutralized by antibodies to other cytokines that induce B cell differentiation. We now report that 446-BCDF stimulation of peripheral B cells results in the activation of STAT 1, and to a lesser degree, STAT 3.

Aim: To study the activation of Ig transcription elements by our novel cytokine.

Methods: We employed an electrophoretic mobility shift assay (EMSA) of whole cell lysates from B cells stimulated with 446-BCDF and a DNA probe that contains the consensus binding sequence of STAT 1 and STAT 3, to access the DNA binding elements associated with the probe. Supershifts and western blots were used to confirm the identity of the proteins.

Results. The EMSAs revealed the activation of both STAT 1 and STAT 3. STAT activation could not have resulted from contaminating cytokines in our BCDF prep, since neutralizing antibodies to STAT activators IL-10 and IL-6 did not ablate the signal. Anti-IFNg did reduce, but did not ablate the STAT 1 signal, verifying a small contamination of IFNg in our BCDF prep. Further studies were done using antibodies against these transcription factors. Supershift analysis revealed that the STAT 1 was the major DNA binding protein and the STAT 3 a minor contributor. In addition, the same B cell lysates were analyzed by western blot and probed with anti-phospho-STAT 3. This experiment confirmed the activation of STAT 3.

Conclusions: STAT 1 and STAT 3 are activated by the novel B cell differentiation factor 446-BCDF. The importance of these proteins in the transcription of immunoglobulin is now under investigation.

gp180, a Novel CD8 Ligand Expressed by Intestinal Epithelial Cells, Inhibits the Activation and Priming of Cytolytic T Cell Responses. K. Becker[1], C. Korsten[1], N. Campbell[1], T. Moran[2], and L. Mayer[1]. [1]Immunobiology Center and [2]Department of Microbiology, Mount Sinai School of Medicine, New York, NY.

gp180 is a novel CD8 ligand expressed by normal intestinal epithelial cells (IECs); it appears to selectively activate CD8+ suppressor T cells in IEC:T cell co-cultures. Since purified gp180 binds to CD8 at sites that are distinct from where classical class I binds, we wanted to determine whether this molecule might affect classical cytolytic T cell priming and effector function. Purified gp180 was added to allo-CTLs during a 4-hour cytolysis assay. While mAbs to CD8 and MHC I completely inhibited killing, gp180 mediated inhibition was negligible (15%) and comparable to the glycoprotein control CEA. These findings were confirmed using IEC targets (HT29), expressing native gp180, in an influenza-driven cytolysis assay. Influenza-infected HT29 cells were readily killed when HLA matched primed anti-flu CTLs were used. We then added purified gp180 to T cells at the onset of the priming culture using influenza-infected PBMC as stimulator cells. gp180 completely inhibited the activation of anti-flu CTLs. These results were extended using 2 cell lines. HT29 cells were flu-infected and used to activate an anti-flu response in HLA-A9 matched PBT cells. While normal APCs could prime a response, no similar activation was seen when HT29 cells were used. HT29 cells were then transfected with HLA-A*0201 used to prime an A2 restricted anti-flu response. Similarly, no activation of anti-flu CTLs was detected. These data suggest that IECs can process viral Ags appropriately (i.e., they can serve as targets for CTL responses) but that the expression of surface molecules such as gp180 may alter the ability of either primary or memory CTL responses to be generated. gp180 effects appear to be in the inductive rather than the effector phase.

Infectious Diseases

Hydatid Cyst Disease: A Clinical Vignette and Review of the Literature. N. El-Dairi, A. Alshrouf, and M. Rabbat. Department of Medicine, St. Joseph's Hospital and Medical Center, Paterson, NJ.

Hydatid cyst disease is a parasitic infection caused by *Echinococcus granulosus*. It remains a serious health problem in many parts of the world, especially in the Mediterranean countries.

We report a case of a 26-year-old native Macedonian male who was brought to the emergency room in a state of acute respiratory distress. He was found to have an oxygen saturation of 47% at respiratory rate of 37/min; 100% oxygen failed to increase his saturation to more than 75%, so he was subsequently sedated, paralyzed, and intubated. His history indicated that he was recently diagnosed in Macedonia with liver cyst, and was to have surgical evaluation as an outpatient shortly after admission to the hospital. Chest x-ray on admission to the hospital showed a large cyst occupying the right lower lobe, and x-rays taken later showed air filling the cyst. Other diagnostic measures, including CT-scan of the abdomen, were normal. The patient was evaluated by thoracic surgical consultant, and the diagnosis of a ruptured lung hydatid cyst was made. The patient was taken to the operating room, where he underwent thoracotomy and lobectomy and was started on albendazole. The patient improved quickly and was discharged from the hospital after one week. He was continued on albendazole for two more weeks.

With recent events in the Balkans, where hydatid cyst disease is endemic, and with the fact that many people from that area might be coming to live in the United States, we hope that this clinical vignette will help health professionals to recognize, treat, and prevent this disease.

Acute Suppurative *Salmonella* Type B Thyroiditis Associated with Hyperthyroidism in a Patient on Immunosuppressive Therapy for Crohn's Disease. J.L. Galan, S. Tummala, J. Farkas, and W. Baddoura. Division of Gastroenterology, St Joseph's Hospital and Medical Center, Paterson, NJ; and Seton Hall University School of Graduate Medical Education, South Orange, NJ.

Introduction: Immunosuppressive drugs play a significant role in the management of Crohn's disease. Opportunistic infections are known complications of such therapy. We present an unusual case of thyroid abscess resulting from long term-use of immunosuppressants.

Case Report: The patient was a 38-year-old diabetic female maintained on 6-mercaptopurine and corticosteroids for active Crohn's disease. She presented with neck swelling, dysphagia, and tremulousness, and was found to have hyperthyroidism associated with a thyroid abscess. Blood and abscess cultures grew *Salmonella* type B. The patient improved after drainage and appropriate antibiotic therapy. Thyroid studies were normal when she was checked three weeks after discharge.

Discussion: Bacterial infections of the thyroid gland are rare and potentially life threatening. If one excludes underlying anatomic defects and previous thyroiditis, the most likely setting in which one may encounter pyogenic thyroiditis is in immunocompromised hosts. Review of the literature reveals one case report of pyogenic thyroiditis due to *Salmonella enteritis* in a patient with acquired immune deficiency syndrome. We strongly suspect that the combination of active colonic inflammation and immunosuppressive therapy contributed to this unusual opportunistic infection in our patient.

Conclusion: To our knowledge, this is the first report of acute suppurative thyroiditis due to *Salmonella* type B in a patient with Crohn's disease on immunosuppressive therapy.

Program to Reduce Usage of Vancomycin: Impact on Antimicrobial Resistance. M.H. Mendelson, F. Wallach, L. Finkelstein, C. Petrec, S. Jones, G. Kogan, G. Papanicolaou, A. Gurtman, P. Duncsak, M. Levin, and M. Klotman. Mount Sinai School of Medicine, New York, NY.

Aim: In an effort to promote judicious usage of vancomycin, an antimicrobial utilization pilot project was initiated by the departments of epidemiology, infectious diseases (ID) and pharmacy at an 1100-bed metropolitan hospital.

Method: Use of vancomycin (i.v. and per os [po]; total grams, g/100 patient days) and nosocomial vancomycin-resistant enterococci (VRE) incidence (new clinical cases excluding urine/1000 pt. days) were analyzed for a baseline and post-intervention period: A - baseline - 7/97 – 5/98, B - post-intervention analysis - 8/98 – 3/99. Interventions included development, distribution and training of Medical Board-approved usage guidelines; daily (weekday) microbiologic laboratory review of all patients on vancomycin; as indicated, daily chart reviews by ID attendings, and direct communication of recommendations for alterations in treatment if usage was not consistent with approved guidelines or other clinical indications.

Results: Results of the pilot are illustrated in Table.

TABLE
Vancomycin Usage

	A – (July '97 – May '98)		B – (Aug '98 – March '99)	
	gm/100 pt days	incidence of VRE	gm/100 pt days	incidence of VRE
MSH	17.2	0.67	12.6	0.58
Oncology I	32.5	0.72	16.0	0.17
Oncology II	39.5	1.16	31.7	0.53
Cardiac Surgical ICU	94.1	2.4	72.4	1.7
Cardiac Surgical	30.5	0.5	15.4	0.15
Surgical ICU	40.3	4.87	33.4	4.1
Medical ICU	37.4	3.57	35.3	5.64

Results in the Medical ICU were not comparable: vancomycin IV (37.4, 35.3), VRE (3.57, 5.64).

Conclusion: At The Mount Sinai Hospital, the vancomycin utilization program appears to have reduced the incidence of VRE in those units in which the amount of vancomycin administered was reduced. The impact that changes in other antimicrobial usage patterns may have on the incidence of VRE also needs to be evaluated.

Internal Medicine

Follow-up of Inpatient and Outpatient Endoscopic Biopsy Results in Elmhurst Hospital Center (EHC). S. Banerjee[1] and A. Lyman[2]. [1]Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Residency Program and [2]Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Background: There have been anecdotal reports at EHC of positive biopsy results for which a responsible M.D. could not be identified.

Aim: This study was conducted to determine whether endoscopic biopsy results are available in the chart and if they are appropriately followed up.

Method: At EHC, bronchoscopy, colonoscopy, sigmoidoscopy, and esophagogastroscopy are performed in a dedicated endoscopy suite. Medical record numbers of all patients who had biopsies done during the months of March–May, 1998 were obtained from the computer database of the endoscopy suite. A systematic random sample was obtained by taking every third qualifying patient. Each patient's chart was reviewed for presence or absence of note on biopsy procedure, official biopsy report from the Pathology Department, and acknowledgment of the biopsy report by any physician within a 3-month period from the date the biopsy was performed. A biopsy result is considered not acted upon if (a) there is a procedure note mentioning a biopsy being done, or (b) there is an official biopsy result in the chart, and (c) there was no acknowledgment of the biopsy report by any physician.

Results: A total of 56 charts were reviewed: ten (18%) patients did not have an official biopsy report in the charts; however, all of these patients were inpatients, and physicians acknowledged all of their biopsy results. Only 1 (10%) of these 10 patients had a normal biopsy result. Of the total sample of 56 patients, 21 patients (38%) did not have their biopsy report acknowledged by any physician, although 19 (90%) of these did have their biopsy reports in the chart. Nineteen patients (90%) had their procedures done as outpatients; 13 (61%) patients had a normal biopsy report. Seven of nine (78%) bronchoscopic biopsy results were unavailable in the charts.

Conclusions: It appears that physicians do not always acknowledge biopsy results in the chart, or that the results may not always be available in the charts in a timely manner. Patients whose procedures were performed as outpatients appear to be at higher risk for non-acknowledgment. The system of handling biopsy documentation may need to be reviewed. Biopsy results delivered via the computer information system may yield better tracking. More extensive study is needed to see if acknowledgment of the biopsy report by the physician(s) improves with conversion to an electronic medical record.

Lipid Profile in Patients from Indian Subcontinent, Further Results. S. Parikh[1] and A. Lyman[2]. [1]Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Residency Program and [2]Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Background: Studies have shown that people of Indian-subcontinent ancestry are at higher risk for coronary artery disease and for more severe disease at a younger age than any other ethnic groups in the United States (US) and elsewhere.

Methods: Medical Primary Care Clinic (MPC) at Elmhurst Hospital Center serves many patients of South Asian ancestry (Indian/ Pakistani, Bangladeshi and Caribbean patients of Indian ancestry [CPIA]). A study was conducted to examine lipid profiles from these patients. Results of the first fifty patients have been reported (1); data on an additional eighty patients are presented in this report. The methodology was unchanged. These data were compared with data from the general US population and from a healthy rural Indian population (HRIP) (2). Chi-square analyses was performed using EpiInfo software to compare proportions.

Results: Cholesterol level of >240 mg/dL was seen in 43% of CPIA, (compared to 63% in previous study), 24% of Indian/Pakistani and 21% of Bangladeshi patients as compared to 8% of HRIP. LDL level of >160 mg/dL was seen in 30% of CPIA (compared to 54% in previous report), 11% of Indian/Pakistani and 25% of Bangladeshi population as compared to 67% of HRIP. HDL level of <35 mg/dL was seen in 37% of Bangladeshi, 22% of Indian/Pakistani and 19% of CPIA patients as compared to 29.7% of HRIP. Triglyceride level of > 400 mg/dL was seen in 4% of Indian/Pakistanis, 2% of Bangladeshi and 0% of CPIA patients as compared to 0.7% of HRIP. Although the original sample showed a statistically significant risk of having cholesterol level of > 200 mg/dL for CPIA (odds ratio 9.5), odds ratio in larger sample was 1.3 and this was no longer statistically significant.

Conclusion: As compared to HRIP, the immigrant Indian population had higher cholesterol, LDL and triglyceride levels; HDL level <35 mg/dL was seen more frequently in HRIP than in immigrant Indians. In comparison to the previous report of fifty patients, this combined study of 130 patients does not show a significant difference in lipid profiles of South Asian patients and CPIA. A larger study is needed to confirm these findings and to investigate the associated environmental and dietary factors.

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***Helicobacter pylori* Infection in Peptic Ulcer Disease, Elmhurst Hospital Center (EHC). S.** Ibrahim[1] and A. Lyman[2]. [1]Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Program and [2]Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Helicobacter pylori (HP) plays a principal role in the pathogenesis of peptic ulcer disease (PUD); 45–100% of patients with duodenal ulcers and 75–85% of patients with gastric ulcers harbor the organism. Infection may be associated with acute complications of PUD, as well as long-term sequelae like recurrence of PUD and gastric carcinoma. In the United States (US), rates of *H. pylori* increase with low socioeconomic status, increasing age and residence in custodial institutions, and are higher in blacks and Hispanics. In developing countries, *H. pylori* is generally acquired in childhood; prevalence rates are much higher than in the US.

Aim: To examine factors associated with *H. pylori*-positivity in PUD at EHC.

Methods: Medical records were reviewed for all patients who underwent esophagogastroduodenoscopy (EGD) for dyspepsia and/or hematemesis from January, 1998 to March 1999. From a chronological list of those patients diagnosed with PUD who underwent a diagnostic test for *H. pylori* (biopsy and/or serology), every fourth patient was selected. Demographic and clinical variables were extracted. Insurance status was noted as an indicator of socioeconomic status. Complications were defined as serious recurrent bleeding or need for major surgical procedure.

Results: A total of 1101 patients underwent EGD, of which 164 patients (14.9%) had PUD and a test for HP. Forty-two patients (25.6%) were selected. Of these, 27 (64.3%) had HP infection: 19 (70.3%) newly diagnosed by positive biopsy on this EGD, 1 (3.7%) with a positive biopsy despite prior treatment, and 7 (26%) who had been successfully treated. Further review of the charts of the 15 HP-negative patients revealed 9 (60%) had a history of NSAID use. Infected patients comprised 12 of 18 Hispanics (66.7%), 9 of 16 Asians (56.3%), 4 of 5 whites (80%), and 2 of 3 African-American patients (66.7%). Of 23 uninsured patients, 9 of 12 Hispanics (75%), and 6 0f 11 Asians (55%) had HP infection. Gastrointestinal bleeding was the presenting symptom in 25 patients (59.5%); 13 of these (52%) were positive for HP. Of 20 currently infected patients, 14 (70%) had a complication vs. 12 of 22 (55%) uninfected patients (odds ratio = 1.94, chi-square = 1.1, p = NS). Fourteen of 20 currently infected patients (70%) experienced relief of symptoms after anti-HP therapy; three (15%) were lost to follow-up.

Conclusions: A substantial proportion of patients with PUD on EGD required treatment for *H. pylori* infection. Prevalence may differ by nationality, socioeconomic class, age and other variables; a larger sample is needed to further delineate the risk of infection in the multi-ethnic, predominantly low-income population served at EHC. In a population with high prevalence, early and aggressive measures to diagnose infection may be warranted.

Likelihood of Coronary Artery Disease (CAD) in Patients Admitted to Elmhurst Hospital Center (EHC) with Chest Pain (CP): Racial and Gender Differences. S.Aytug[1] and A. Lyman[2]. [1]Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Residency Program and [2]Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Chest pain (CP) is one of the most common reasons for hospital admission. In an ethnically diverse inner city hospital, initial evaluation of patients from different cultures and genders can be difficult due to language barriers and possibly different clinical presentations.

Aim: To determine whether race and gender are significant determinants of the presence of CAD in-patients with CP.

Methods: From January 1, 1996 to April 30, 1998, all patients who were admitted to EHC with a CP-related diagnosis were identified, and a sample was selected using random numbers generated by EpiInfo software. Presence of CAD is defined as having a positive exercise thallium stress test, present or past myocardial infarction, positive cardiac catheterization, prior percutaneous transluminal coronary angioplasty or coronary artery bypass graft. CAD was classified as newly diagnosed or prior CAD. Absence of CAD is defined as having a negative stress thallium test, normal coronary arteries.

Results:

1. There were 1759 admissions; 150 were selected for the sample, of these, 33 (22%) did not meet inclusion criteria. Of the remaining 117, 63 had CAD (53%), 54 (47%) did not. Of the 63 CAD patients, 31 (49%) were newly diagnosed CAD and 32 (51%) had prior CAD.
2. In the new CAD group, there was no significant difference according to gender. The odds ratio of a male having new CAD was 0.81 (95% CI: 0.3, 2.21), p = NS. The presence of CAD was not associated with race (chi-square = 1.33, p = NS).
3. Of smokers, the odds ratio of females having new CAD vs. no CAD was 3.08, p = NS.
4. Of the patients who had CAD, the odds ratio for females having diabetes was 2.35 (95% confidence interval = [0.88, 6.36]; chi-square = 3.58, p = 0.058 [NS]); the odds ratio for males being smokers was 2.48, p = NS.

Conclusions:

1. Patients admitted with CP and subsequently diagnosed with CAD were just as likely to be of either gender or any ethnic group.
2. Forty-seven percent of patients admitted with CP did not have CAD.
3. Among smokers without known CAD, gender was not statistically significantly associated with being diagnosed with CAD.
4. Among those with CAD, females were more than twice as likely to be diabetic (this approached statistical significance).

Management of Hyperlipidemia in the Medicine Primary Care Clinic (MPC) at Elmhurst Hospital Center (EHC).

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The National Cholesterol Education Program (NCEP) has developed recommendations for the management of patients with hyperlipidemia.

Aim: To study identifying patients with hyperlipidemia, the implementation and length of non-pharmacologic therapy, and the initiation of pharmacologic therapy in compliance with the NCEP guidelines.

Methods: A database of all patients with a Low Density Lipoprotein (LDL) of $160 mg/dL seen in different clinics between January 1, 1995 and December 30, 1996, was obtained; from those patients followed in the MPC clinic, every tenth patient was selected. One hundred charts were reviewed for age, ethnicity, gender, number of risk factors for CAD, time period between diagnosis of hyperlipidemia and the start of non-pharmacologic and pharmacologic therapy and compliance with NCEP guidelines.

Results: The total number of patients was 100. Gender: 28% male and 72% female. Ethnicity (male patients): Caucasian 7 (25%), East Asian 3 (10.71%), Hispanic 10 (35.70%), South Asian 6 (21.42%), Other 2 (7.14%). Ethnicity (female patients): African-American 10 (13.88%), Caucasian 6 (8.33%), East Asian 3 (4.16), Hispanic 35 (48.61%), South Asian 8 (11.11%), and Other 10 (13.88%). Fifteen percent (15%) of patients had documented CAD, 85% did not. Risk factors for CAD: 0: 19%, 1: 11% and 2 or more: 70%. The start date of non-pharmacologic therapy was not documented in 47 (47%). The time frame between start of pharmacologic therapy and initial documentation of diagnosis was stratified: < 3 months: 5, 3–6 months: 12, 6–12 months: 14, 12–24 months: 14, 24–36 months: 9, 36–48 months: 0, > 48 months: 7, not documented: 13 and not started: 26. Of 100 patients, 74 were started on pharmacologic therapy, 26 were not. Of the latter, 12 had improved LDL with non-pharmacologic measures, 2 charts had insufficient data; the remaining 12 were then stratified on the basis of risk factors (zero: 2 patients, one: 0 patients, 2 or more: 9 patients and one patient with documented CAD). The two patients with no risk factors had LDL of >190 mg/dL, the only patient with CAD had LDL of 160 mg/dL, the nine patients with 2 or more risk factors had LDL >160 mg/dL. Ethnicity of these twelve patients was Hispanic 6 (50%), African American 2 (16%), Caucasian 2 (16%), other 2(16%). Gender distribution: male 1 (9%) and females 11 (91%).

Conclusions: Despite knowledge about the effects of hyperlipidemia and the need for early treatment, there are still patients not receiving appropriate therapy as per NCEP guidelines. Physicians have yet to embrace NCEP guidelines; medical education should include training on treatment of hypercholesterolemia.

Patient Satisfaction with Education at the Medical Primary Care Clinic of Elmhurst Hospital Center (EHC).

M.G.O. Rabin[1], A. Lyman[2], and L. Ares[2]. [1]Housestaff Alumnae, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Residency Program and [2]Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Patients obtain information on medical conditions and their treatment from many sources. Their satisfaction with education obtained at the Medical Primary Care (MPC) Clinic at EHC may influence their overall perception of quality of care.

Aim: To study (a) sources of information on medical conditions and treatment, and (b) evaluate knowledge developed from and satisfaction with patient education at MPC.

Methods: A questionnaire was developed to collect information on demographic variables, educational attainment, knowledge about the patient's medical condition and medications, sources of such knowledge, and factors affecting the comfort of patients in discussing compliance and psychosocial issues with the primary care physician. The questionnaires were distributed at session registration to all English-speaking patients known to MPC. Patient identifiers allowed linkage to the surveyed record, but confidentiality was assured. Diagnoses and medications indicated by patients were confirmed by review of the medical record.

Results: Ninety consecutive surveys were distributed. Eighty-one (90%) questionnaires were returned. Of respondents, 44% were over 60 years, 62% were female, 32% were Black non-Hispanic, 27% were Hispanic, 19% were White non-Hispanic, 17% were Asian, 5% ethnicity not given. Fifty-five percent (55%) had a high school or greater educational attainment; 7% had a grade school education and 7% had never attended school. Seventy-two percent (72%) stated they knew what medical conditions they had, 19% did not know, and 9% did not answer. A variety of sources of medical information were provided by patients; 59 (66%) stated that their main source was their physician, 18% indicated print media, and 13% indicated TV. Sixty-five percent (65%) knew the medications they were taking, but only 22% knew the possible side effects. Those with higher educational attainment were more likely to know their conditions and medications. Sixty percent (60%) stated they had adequate time to tell their physician all their complaints; 57% felt they were given enough information about their medical condition and 25% did not. Fifty-three percent (53%) felt comfortable discussing alternative medicines with their physician, 40% felt comfortable discussing the influence of their religious beliefs on their compliance with medical treatment and 49% were comfortable discussing personal problems affecting their health; 21% had discussed or planned to discuss advance directives with their physician. Seventy percent (70%) were satisfied with their physician. Female patients were more likely to be comfortable in discussions with the physician, (OR = 2.77, chi square = 4.09, $p < 0.05$.).

Conclusions: Subgroup analyses were limited by the study's sample size, and patient participation may have been affected by the lack of anonymity of the response. Further investigation is warranted.

Factors Associated with Appointment Compliance at Medical Primary Care Clinic (MPC), Elmhurst Hospital Center (EHC).

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Failure to keep an appointment may affect care of the patient, and also influence productivity of primary care sites. Data are inconclusive regarding the association of gender, race, age, time of visit, language barriers, and other factors with appointment compliance.

Aim: To study demographic and other variables of patients who miss appointments in a public hospital clinic with an ethnically diverse patient population.

Methods: A list of all patients scheduled to visit the Medical Primary Care Clinic (MPC) during a representative week was obtained. Patient characteristics were obtained from the computerized database. Patients who missed an appointment were contacted by telephone by the investigator or an interpreter for Spanish- or Mandarin-speaking patients. Frequencies were tabulated using Systat software; odds ratios were calculated and chi-square and Fisher's exact test were performed using SPSS and EpiInfo.

Results: There were 728 scheduled visits in the selected time period; 464 visits (63.7%) were kept and 264 (36.3%) were missed. A total of 113 males (39.1%) with appointments failed to keep them, as compared to 151 females (44.5%) (odds ratio [OR]=1.25, chi-square = 2.02, p = ns). There was no statistically significant difference in appointment-keeping based on race/ethnicity (chi-square = 8.72, p = ns) or by English-speaking status. The OR for missed appointments for patients new to MPC was 1.91 (chi-square = 7.5, p = 0.006); for patients with psychiatric diagnoses, the OR was 1.93 (chi-square = 8.09, p = 0.005); for daytime appointments vs. evening, the OR was 2.24 (chi-square = 4.65, p = 0.031). Of those who missed appointments, 154 (57.3%) could be contacted by telephone; 110 (42.7%) could not be contacted. Of the 154, 99 (64.2%) spoke English and 55 (35.8%) did not. Reasons for missing appointments were: forgot (20.6%), had to work (18.8%), perceived a language barrier (14.9%), and other reasons (32.1%); 13.6% had changed their appointment, but this fact was not noted in the MPC computer scheduling system.

Conclusions: A substantial proportion of appointments is not kept at MPC, especially by new patients, patients with psychiatric diagnoses, and patients with daytime appointments. Compliance with appointments, an important factor in providing primary care, may be affected adversely by many factors in a low-income, multi-ethnic population. Further research is needed to elucidate modifiable risk factors of missed appointments.

Complications of Central Venous Catheterization in a Medical Intensive Care Unit and the Necessity of a Postprocedural Chest Radiograph: A Retrospective Study. F. Mankarios[1], S. Baffic[2], D. Benz[2], E. Erickson[1], and M. Moore[2]. [1]Department of Medicine, St. Joseph's Hospital and Medical Center, Paterson, NJ; and 2University of Medicine and Dentistry, Newark, NJ.

The placement of a central venous catheter (CVC) is one of the most common procedures that have been associated with low morbidity and mortality when performed in the medical intensive care unit (MICU). It has been a routine practice to order a postprocedural chest radiograph to ensure the absence of complications.

Aim: To study the incidence and complications of the CVC in the ICU population and correlate that with the cost and necessity of the postprocedural chest radiograph.

Methods: We retrospectively reviewed the charts, postprocedural radiographs and reports of the patients in the MICU who were subjected to a triple lumen CVC at St. Joseph Hospital and Medical Center during 1997 and 1998. Our population consisted of 131 subjects, 49.6% female and 50.4% male. The ages of the subjects ranged from 19 to 94 with a mean age of 58.4%. The postprocedural complications were 3.9%. They included one case of pneumothorax (0.75%) that required the placement of a chest tube. Unsuccessful catheterization was encountered in 3.8%. The review of 131 postprocedural radiographs showed one pneumothorax and a malposition rate of 5.3%.

Conclusion: Complications associated with CVC were limited and comparable to the previous studies. We do not advocate the performance of a postprocedural chest radiograph routinely.

Epidemiology of Lymphomas in Elmhurst Hospital Center (EHC). A.R. Thummala[1] and A. Lyman[2]. [1]Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Residency Program and [2]Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Lymphomas are heterogeneous malignancies arising from T or B cells. Studies have shown that the risk of lymphoma among HIV patients is rising, possibly due to increasing survival of the population treated with highly active anti-retroviral therapy.

Aim: To study the patterns of lymphomas in EHC.

Methods: A retrospective cohort study was done. All patients who were diagnosed with lymphoma from January 1994 to December 1997 were included. Cancer registry data and patient charts were reviewed for demographic and clinical data. The list of patients was then compared to the registry of the Infectious Diseases Clinic in order to identify any additional patients known to be HIV-positive. Frequencies were tabulated and Epi-Info was used to compare proportions.

Results: One hundred patients were diagnosed with lymphoma during the study period. More cases occurred in males (62%); this was true for all ethnic subgroups except Asians. Cases were more likely to be White or Hispanic, and the peak age group was between 30–40. Thirty nine percent (39%) presented with advanced disease; Whites constitute 46.15% of this group. Thirty percent (30%) of the patients were HIV positive, with Hispanics being in greater proportion (46.60%) compared t other groups. Lymph nodal disease accounted for 63% of the cases in th group of HIV-negative or HIV-unknown compared to 33% in the HIV positive group. CNS lymphomas comprised 56% of the cases in the HIV positive group, compared to 2.9% in the other group (HIV-negative and unknown). In the HIV-negative/unknown group, 29.62% died, compare to 66.66% in the HIV positive group (through December 1998). HIV related lymphomas decreased from 10 (38.4%) in 1994 to 4 (16%) i 1997. On comparing the data between 1994 and 1997, we noted a highl statistically significant decrease in the proportion of HIV-related lymphomas (chi-square = 19.52, p = 0.0058).

Conclusions: These results suggest that the risk of lymphoma is decreasing among HIV-positive patients (anecdotal evidence indicates this may be seen at other New York City clinical sites as well). However, earlier access to insurance coverage may affect where patients seek care, and thus these results must be viewed with caution. Additional studies are needed to further define this risk.

Clinical Predictors of Mood and Anxiety Disorders in Medical Primary Care Clinic (MPC) Patients. G. Tangarorang[1], S. Mariano[1], L. Ares[1], and P. Leong[2]. [1]Department of Primary Care-Internal Medicine and [2]Department of Psychiatry, Elmhurst Hospital Center, Elmhurst, NY.

Mood and anxiety disorders are among the most common mental disorders in the community and in primary care clinics (1). They cause significant patient morbidity and mortality and impose a heavy economic burden (2). These disorders are largely undiagnosed and therefore undertreated by primary care providers (3).

Aims: To identify clinical predictors of mood and anxiety disorders in medical primary care clinic patients.

Methods: Patients in MPC were interviewed to collect demographic variables and were administered the Primary Care Evaluation of Mental Disorders, PRIME-MD, a validated instrument to determine the presence or absence of mood and/or anxiety disorder (4). Major medical diagnoses, medications and clinic visits for all participants were then extracted from the patients' chart. Statistical analyses were performed on data from groups with and without these disorders, using Student's t test for comparing means and Fisher's exact test to compare proportions.

Results: Thirty-four of 88 randomly selected patients met the inclusion criteria and agreed to participate. A mood or anxiety disorder was present in 12 (35%). Of these, 6 (50%) had a known disorder, (5 of them were under therapy) while the other 6 (50%) were diagnosed by the investigators. Six (50%) had pure mood disorder, 3 (25%) had mood and anxiety disorder, 1 (8%) had mood and binge eating disorder and 2 (16%) had pure anxiety disorder. Patients with mood disorders reported more recent stressors (75% vs. 4%, $p < 0.001$), physical complaints (7.33 vs. 4.27, p = 0.006), history of drug use (16% vs. 0%, p = 0.036) and suicidal tendencies (32% vs. 0%, p = 0.011). There was no significant difference among patients with and without these disorders in terms of age, race/ethnicity, education, smoking habits, alcohol abuse, family history of any psychiatric disorder, sense of well-being, perceived level of care, number of concurrent major medical diagnoses or number of clinic visits.

Conclusion: Mood or anxiety disorders are commonly found among patients in the MPC. Predictors of these disorders (multiple physical complaints, recent stressors, drug use and history of prior suicidal ideation/attempt) should trigger further evaluation.

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Microscopic Hematuria, Medical Primary Care Clinic (MPC), Elmhurst Hospital Center (EHC). M. Alam[1] and A. Lyman[2]. [1]Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Residency Program and [2]Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Normal individuals may excrete some red blood cells (RBC) in the urine. Hematuria, whether gross or microscopic in nature, may be a sign of serious underlying urologic disease including malignancy. Microscopic hematuria (MH) is an incidental finding that is frequently discovered as part of routine examination. Three or more RBC/high-power field on at least two of three properly collected and properly performed urinalyses (U/A) require evaluation. In studies of adults with MH, the likelihood of finding urologic cancer is 5%, versus 23% in those patients with gross hematuria.

Aim: To examine demographic and clinical variables associated with MH at EHC.

Methods: A retrospective cohort study of microscopic hematuria was done in MPC. A list of all patients followed by a subset of providers was obtained. Charts were reviewed, and demographic data were collected on age, sex, ethnicity, comorbid risk factors, duration of microhematuria, number of abnormal U/A, findings on U/A, renal function, evaluation/investigation done, and final diagnosis. Of approximately 500 patients, 75 had MH; of these, 45 charts (60%) were available for review.

Results: Twenty-nine (29) patients were over 55 years old (64.44%), 38 patients were female (84.44%), 27 patients were Hispanic (60%), 25 patients had hypertension, (55.55%), 26 patients had MH for more than 24 months (35%). Urine cytology was performed on 13 patients, renal ultrasound on 28 patients, intravenous pyelography (IVP) on 4 patients, computed tomography on 3 patients, cystoscopy on 6 patients, renal biopsy on 2 patients. Final diagnosis: 1 patient (2.2%) was found to have renal cell carcinoma, 2 patients (4.4%) had glomerulonephritis (GN) (1-IgA nephropathy, 1-membranous GN), 1 (2.2%) each with interstitial nephritis, nephrolithiasis, and prostatic hyperplasia, 3 patients (6.6%) with renal cysts. Eight patients were found to have other diagnoses (1 patient with Evan's syndrome, 5 patients with recurrent urinary tract infection had microhematuria when asymptomatic, 2 patients with probable diabetic nephropathy). No pathology was found in 6 patients (13.3%). No patient was found to have bladder cancer. Seven patients had pending evaluation (15.55%). Sixteen patients (35%) had no evaluation of abnormal U/A.

Conclusions: A substantial proportion of patients did not have diagnostic evaluation of MH, which may be a clue to serious urologic disease, including malignancy, and should be evaluated.

Acute Myocardial Infarction due to Mediastinal B-Cell Non-Hodgkin's Lymphoma in a Young Woman. K. Chennapragada[1], V.M.K. Bhaskarabhatla[2], and M. Kelly[1]. [1]Saint Joseph's Hospital and Medical Center, Paterson, NJ; and [2]Internal Medicine Associates, Mount Sinai School of Medicine, New York, NY.

A 26-year-old woman was brought to the emergency room (ER) in a state of shock (BP 71/28 mm Hg) and acute respiratory distress. She had a long history of autism, seizure disorder, and treatment by phenytoin and carbamazapine. In addition, there was a one-month history of progressive dyspnea, cough, anorexia, fatigue and weight loss. Chest radiograph and computed tomography (CT) scan had revealed a large mediastinal mass, infiltrating the heart and the great vessels, with pleural effusion. She had electrocardiographic signs of acute antero-lateral myocardial infarction with posterior extension and inferior subendocardial ischemia (Q waves in L1, aVL, V2, and V3; poor progression of R waves in precordial leads; ST segment elevations > 0.20 mV in leads L1, aVL, V4 -V6; ST segment depressions in L2, aVF, and V1; and inverted T waves in leads L2, L3, and aVF). An echocardiogram in the ER showed antero-apical akinesia, focal anterior pericardial effusion, and a solid mass in the pericardial cavity. Her cardiac enzymes were markedly elevated, and there was severe hypoxia (paO_2: 22 mm Hg), hypercapnia ($paCO_2$: 35 mm Hg) and acidosis (arterial blood pH: 7.17). She had immediate artificial ventilation and was transferred to the intensive care unit. Following informed consultations with her family, a "Do-Not-Resuscitate" decision was made. On day 9, she suffered cardiac arrest and died.

At autopsy, the mediastinal mass was found to be a B-cell non-Hodgkin's lymphoma with malignant lymphomatous infiltrations of the heart and the coronary arteries. The ventricles showed extensive areas of infarction and necrosis of the myocardium.

Great progress has been made in the treatment of lymphomas in recent decades by radiotherapy and/or chemotherapy, with significant cure rates even in the advanced stages. Patients who relapse following treatment have been known to present with lymphomatous pericardial and cardiac infiltration, especially in the terminal stages. However, to our knowledge, this was the first known instance of acute myocardial infarction due to lymphomatous infiltration as an initial presenting feature in a previously untreated patient with lymphoma. Had the nature of her disease been recognized ante-mortem, emergency radiotherapy and/or chemotherapy might have been successful in altering the course of her disease.

Xanthogranulomatous Pyelonephritis: A Case Report with Critical Review. I.G, Abadeer and R. Marton. Department of Internal Medicine, St. Joseph Hospital and Medical Center, Paterson, NJ.

We report a case of unilateral xanthogranulomatous pyelonephritis (XPN) in an adult, diagnosed after right nephrectomy, followed by a review of the literature on XPN.

Case Report: A 44-year-old man with a history of hemophilia A was admitted with complaints of fever and suprapubic pain for 1 week. Nine years prior to admission he had developed complications resulting from a lumbar puncture. His medical history also included asthma, depression and arthritis. The patient's medications were lactulose, acetaminophen, Duragesic®, patch, Dilaudid®, Ativan®, and Cipro®. On physical examination, he had temperature of 103.2°F, a pulse rate of 124/min and blood pressure of 137/86 mm Hg. He was in his usual mental status. He had dry, warm skin and diffuse abdominal tenderness, especially around the suprapubic catheter. Laboratory results showed white blood cell count of 9000/mm_, prothrombin time of 14 seconds, and partial thromboplastin time of 47.2 seconds. Routine urinalysis revealed turbid appearance, large amount of blood and protein, positive nitrite, large leukocytes, >100 RBC, >100 WBC, and many bacteria. Catheterized urine culture had colony count of 100,000 colonies/mL, identifying *Proteus mirabilis* and methicillin-resistant *Staphylococcus aureus*. (The patient was started on IV Vancomycin and ceftazidime, according to sensitivity.) Blood culture was negative. Renal ultrasound showed very thin cortex and hydronephrosis in the right side, no abnormalities in the left side. On IVP, the right kidney was not visualized. No uptake of technetium in the region of the right kidney indicated nonperfused and nonfunctioning right kidney. The patient was given factor VIII one day prior to and ten days after the right nephrectomy. The pathological report showed hydronephrosis with xanthogranulomatous pyelonephritis.

Genitourinary obstruction and urinary tract infection are strongly implicated in the development of XPN. Because the clinical presentation of the disease is variable and nonspecific, it is frequently misdiagnosed either as renal neoplasms, abscesses or tuberculosis. CT scan is the best radiological imaging technique for discovering the extent of inflammation. Diagnosis requires renal tissue for special pathological staining. Lipid-laden macrophages called "xanthoma cells" characterize the disease. Treatment by nephrectomy or partial nephrectomy has been the mainstay of therapy for XPN, although a trial of antibiotics prior to surgery is warranted in cases of focal XPN.

Evaluation of a Community-Based Clinical Experience, and the Resident's Role in Curriculum Development. L.M. Reich and R.A. David. Department of Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

In a previous report, we described the creation of a community-based clinical experience in a primary care internal medicine residency program. The development of this curriculum relied on the residents' assessments of their learning needs and their retrospective identification of learning objectives. The clinical experience consisted of five components: a community-based geriatrics practice, a mobile-van outreach facility, an urgent-care walk-in center, and home visits to homebound geriatrics and AIDS patients.

Aim: To evaluate this curriculum in terms of how well we (1) met clinical learning objectives; (2) helped improve the residents' clinical performance; and (3) achieved the goal of including residents in curriculum development.

Methods: The thirty-six residents (12 per PGY level) who had rotated through one or more of the five components of the community-based clinical experience were surveyed regarding the educational and clinical value of the rotation and their role in curriculum development. Residents were asked to respond to a series of statements along a five-point Likert scale.

Results: Twenty-eight of 36 residents (78%) returned completed surveys. A total of 31 resident-rotations were evaluated (mean of 1.11 sites per resident). Residents gave positive ratings to all components of the curriculum, with Home Care-Geriatrics receiving the highest ranking and Home Care-AIDS the lowest. Despite this, Home Care-Geriatrics received the lowest ranking for "new clinical experience" and Home Care-AIDS among the highest. Home Care-Geriatrics was also ranked highest in terms of causing the residents to "think differently" and "change their attitudes" about "certain clinical situations." The community-based practices (geriatrics and urgent-care center) were ranked as the strongest learning experiences. In terms of their role in curriculum development, residents gave positive responses only for the urgent care center, although overall they felt that their "input was important in terms of curriculum development" (more so for PGY-III's than for PGY-I's).

Conclusions: The addition of community-based clinical experiences provided residents with new learning experiences and resulted in a self-perceived change in clinical thinking and attitude (an independent educational goal of residency training). Overall, the residents felt that they played a significant role in curriculum development, although they could not identify specific aspects of the curriculum for which they felt they had done so. It is not known at this point to what extent the residents' experience in curriculum development contributed to the positive impact of this curriculum on their training.

Training in Nicotine Addiction Treatment in Internal Medicine and Family Practice Residency Programs.

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Studies have demonstrated that physicians feel unprepared to treat nicotine addiction (1); integrating specific training into graduate medical education may improve specific skills and overall efficacy of physicians in this area.

Aim: To ascertain current practices of residency programs, a survey was conducted in conjunction with a program (funded by a Project ASSIST grant to the Coalition for a Smoke-free City/NYC Department of Health) to develop a network of "tobacco control physician liaisons" (residency program faculty who would (a) coordinate training and tobacco control advocacy for their programs, (b) serve as media spokespersons, and (c) provide cessation materials for their institutions' Employees' Health Services).

Methods: A list of all residency programs in internal medicine (IM) and family practice (FP) in New York City was obtained. Each program was sent a packet containing the survey and curricular, scientific and patient education materials. Survey responses were tabulated and frequencies calculated with EpiInfo software.

Results: Sixty-three (63) eligible residency programs were identified and sent packets; 56 (89%) that did not respond were remailed the survey. Fifteen programs (24%) responded to the survey; representing 19 tracks (4 FP, 6 traditional IM, 8 primary care IM, 1 ambulatory care IM). Of fourteen programs, 13 (93%) taught nicotine addiction treatment; 6 (43%) taught 100% of residents; 8 (57%) as part of a formal curriculum, 13 (93%) informally during precutting, 10 (71%) at an occasional lecture. Nine (64%) taught brief counseling techniques, 12 (86%) taught use of pharmacologic agents, 7 (50%) provided curricular materials for physicians (NCI:5, AHCPR:2, American Academy of Family Practice:2, other:2); only 4 (29%) found these useful. Twelve of 15 programs (80%) had had residents who smoked; 10 (67%) had had faculty who smoked; only 2 respondents (15%) had intervened (referral and/or counseling). Three (20%) institutions had smoking cessation groups for employees; and 3 (20%) had groups for patients. The most frequently perceived barriers to training were lack of time, rotation of residents, and perceived failure of cessation by patients; most frequently cited need was for new curricula.

Conclusions: A program offering limited assistance with smoking cessation training is not an effective method of increasing residency program involvement with local tobacco control infrastructure, or for assessing residency program practices. Further study is needed to ascertain and improve graduate medical education in nicotine addiction treatment.

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Epidemiology of *Burkholderia cepacia* Colonization in a Cohort of Cystic Fibrosis Patients.

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Burkholderia cepacia was first recognized as a significant pathogen in the cystic fibrosis (CF) population in 1979. It is known to colonize patients earlier in life than other gram-negative bacteria. Colonization has been anecdotally reported to lead to a more rapid deterioration in lung function, and ultimately death, than would otherwise be expected. We characterize a cohort of 24 patients colonized with *B. cepacia*.

Aim: To evaluate the impact of *B. cepacia* colonization on the clinical course of CF patients.

Methods: A retrospective chart review was undertaken. The Brasfield Scoring System (1) was used to evaluate chest radiographs. It assigns demerit points in each of five categories: nodular densities; linear markings; large lesions (e.g., subsegmental and lobar infiltrates, atelectasis); complications (e.g., pneumothorax); and overall severity. Annual films from up to five years before and five years after *B. cepacia* colonization were evaluated by five independent investigators, blinded to patient name, respiratory status, and date of colonization. Repeat evaluations were completed on three patients to establish an internal intraobserver control. For each patient, a mean of the five observers' Brasfield scores was calculated and recorded.

Results: A total of 24 patients, ages 2 to 31 years, were evaluated. There were 3 sets of siblings. Four patients were colonized with *B. cepacia* for 10+ years; only one of them has died. Another patient, colonized for 2.5 years, has also died. Sixteen (16) patients were colonized with other multidrug-resistant (MDR) organisms (Chart 1). Six (6) patients grew *Aspergillus* species from their sputum. The mean albumin level at time of colonization was 4.2 g/dl (range 3.1 – 5.3). The mean Body Mass Index (BMI) was 19.4 kg/m^2 (range 15.6 – 22.8). The number of hospitalizations per year for each patient before and after colonization was calculated (Chart 2). There was no statistically significant change in the number of hospitalizations after colonization (pre-colonization mean 1 ± 1; post-colonization mean 1 ± 1; $p > 0.5$). Sixty-three percent ($n = 15$) of our patients became colonized with *B. cepacia* in the two-year period November, 1994 to November, 1996, during which all of these patients were hospitalized at least once. Brasfield scores were also evaluated before and after colonization. No statistically significant change in scores was found (pre-colonization mean 18.49 ± 3; post-colonization mean 15.36 ± 3; $p > 0.5$).

Conclusions: We evaluated 24 CF patients colonized with B. cepacia over a 10-year period, during which only two have died. We found that CF patients can become colonized with *B. cepacia* as early as two years of age. Three patients have survived colonization for greater than 10 years. A large percentage of our patients had either a sibling with *B. cepacia* or were hospitalized during a 2-year period when over 60% of our patients became colonized. No significant change in morbidity, in terms of number of hospitalizations or CXR findings, was found after the time of colonization.

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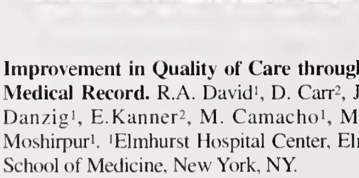

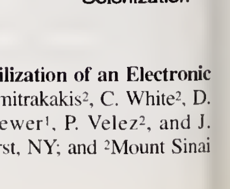

Improvement in Quality of Care through Utilization of an Electronic Medical Record.

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The Joint Commission for Accreditation of Healthcare Organizations requires there to be a summary list in the medical record. This list must include four elements: diagnoses (and problems), medications, allergies, and significant historical data (hospitalizations and procedures). This has been a notoriously difficult task to achieve in hospital settings, due to problems involving chart management.

Aim: To evaluate whether conversion of the chart summary list from a paper record to an electronic medical record would improve compliance with summary list completion. Our site was the ambulatory practices unit of a large acute care municipal hospital with nearly 500,000 patient visits yearly.

Methods: Compliance with summary list completion was monitored before and after the summary list was converted from a paper medical record to an electronic medical record. All four elements of the list were required to be complete in order for compliance to be achieved in any individual record. Charts were sampled in random fashion on an ongoing basis throughout the study in numbers proportional to the visit frequencies of the various primary care and specialty practices at the hospital site.

Results: Before conversion to an electronic medical record, the completion rate for the summary list was 91/2485 x 100 = 3.7% ± 5% (99% confidence interval) over a baseline 3-month period. After all four elements of the summary list were moved to the electronic medical record, the completion rate was 680/680 x 100 = 100% ± 5% (99% confidence interval) over a 6-month period.

Conclusions: Implementation of an electronic medical record led to a substantial and sustained improvement in compliance with summary list completion. This allows immediate access to vital clinical information with much greater reliability. It also satisfies Joint Commission for Accreditation of Healthcare Organizations requirements.

Liver

Characteristics of Oleic Acid Uptake by Rat Adipocytes and Binding to Rat Adipocyte Plasma Membranes Indicate Two Distinct Pathways for Cellular Uptake. D.D. Stump[1], X. Fan[1], and P.D.Berk[1,2]. [1]Department of Medicine, Division of Liver Disease and [2]Department of Biochemistry, Mount Sinai School of Medicine, New York, NY.

Despite identification of seven proteins as putative long-chain (LC) free fatty acid (FFA) transporters, facilitated LCFFA transport mechanisms remain controversial. Others report that LCFFA "flip-flops" very rapidly across synthetic lipid bilayers, with msec T-1/2s, making a need for facilitated transport unlikely (1). However, using the same methods, researchers found that LCFFA uptake by adipocytes, studied at non-physiologic conditions with respect to LCFFA and albumin concentrations, was much slower, with a T-1/2 of ~40 sec (1).

Aim: To determine the mechanisms of LCFFA uptake by adipocytes.

Methods: Rat adipocytes and adipocyte plasma membranes were isolated by standard methods. Initial cellular [3H]-oleate uptake velocity (2) and equilibrium binding studies were conducted at 37°C in the presence of bovine serum albumin (BSA), at LCFFA:BSA ratios of 0.1:1 - 4:1. Unbound oleate concentrations (Ou's) were calculated according to Spector et al. (3).

Results: Both uptake and binding consisted of the sum of a saturable plus a non-saturable component of the form:

$$F(Ou) = P1.Ou/(P2 + Ou) + P3.Ou,$$

where F(Ou) represents either uptake or binding at a given Ou. By assuming that the substrates for saturable and non-saturable uptake, respectively, were the separate LCFFA pools bound either saturably or non-saturably to the membrane, it was possible to calculate rate constants of transmembrane movement of LCFFA by the separate saturable (ks = 2.9 sec-1, T-1/2 = 0.2 sec) and non-saturable (kns = 0.13 sec-1, T-1/2 = 5.3 sec) uptake processes. The calculated ks is similar to others reported for protein-mediated transport; that for non-saturable uptake (kns) is much slower. Both are similar to results in hepatocytes (4).

Conclusions: LCFFA uptake by adipocytes consists of two components: a rapid, saturable process reflecting protein-mediated transport and a slower, non-saturable one reflecting passive "flip-flop."

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Promoter Analysis of Mitochondrial Aspartate Aminotransferase (mAspAT) to Localize Regions Responsive to Adipocyte Differentiation. M.W. Bradbury[1], D.D. Stump[1], and P.D. Berk[1,2]. [1]Division of Liver Diseases, Department of Medicine, and [2]Department of Biochemistry, Mount Sinai School of Medicine, New York, NY.

Mitochondrial aspartate aminotransferase is a well-studied enzyme with a role in nitrogen balance and the malate-aspartate shuttle, which passes reducing equivalents across the mitochondrial membrane. The enzyme is also found on the surface of adipocytes, hepatocytes, and other cells with high transmembrane free fatty acid (FFA) fluxes, and was isolated and described as plasma membrane fatty acid binding protein (FABPpm). Certain fibroblast cell lines, such as 3T3-L1, can be induced to differentiate into adipocytes *in vitro*. During this differentiation there is an increase in FFA uptake, and in the case of 3T3-L1, a large increase in the amount of mAspAT mRNA in the cell and FABPpm on the surface. An increase in gene transcription is a likely source of some of these changes.

Aim: To determine if the mAspAT promoter responds to pre-adipocyte differentiation and identify putative responsive regions or elements.

Methods: We designed a promoter construct containing a zeocin-resistance selectable marker, a secreted alkaline phosphatase (SEAP) reporter gene, and a 1.7 kb fragment of the rat mAspAT promoter. Full-length plasmid and plasmids with deletions of the promoter were transfected into 3T3-L1 fibroblasts with SuperFect® (Qiagen, Santa Clara, CA). Stable transfectants were prepared by Zeocin selection. Individual clones or mixed populations of transfectants were induced to differentiate into adipocytes. Medium was changed every 48 hrs and assayed for SEAP activity. Endogenous phosphatases were inhibited by heat inactivation and l-homoarginine.

Results: Clones of 3T3-L1 bearing the full-length mAspAT promoter construct were analyzed and showed significant SEAP expression in a similar pattern. Expression was increased above background on day 0 of differentiation, followed by a slight increase on day 2, and a significant increase by day 4. The level of expression either remained stable through day 8 or showed a slight decrease. The first two deletion constructs analyzed suggest that there may be negative as well as positive regulatory elements in the promoter. A construct deleted to position −251 showed an increase in expression on day 2, and a decrease to the level of day 0 thereafter. A construct with a longer promoter region, to −441, however, showed no expression above background in six clones analyzed. Further deletion constructs are being constructed and analyzed.

Conclusions: The mAspAT promoter is responsive to pre-adipocyte differentiation. The 1.7 kb fragment produces an expression pattern consistent with studies of mRNA expression. The different expression patterns of deleted constructs suggest that there are both positive and negative regulatory elements within the promoter. Further analysis should locate these elements and allow for the identification of binding sites for either known or novel transcription factors.

Histopathologic Analysis of the Progression to Cirrhosis in Patients with Recurrent Hepatitis C Viral (HCV) Infection after Liver Transplantation. T.D. Schiano[1], M.I. Fiel[2], M.Q. Ye[2], A.D. Min[1], L. Kim-Schluger[3], P.A. Sheiner[3], S.H. Sigal[1,4], S.N. Thung[2], and H.C. Bodenheimer[1]. [1]Division of Liver Diseases, Department of Medicine, and Departments of [2]Pathology and [3]Surgery, Mount Sinai School of Medicine, New York, NY, and [4]Division of Gastroenterology and Gastrointestinal Immunology, Department of Medicine, Columbia University/St. Luke's-Roosevelt Hospital, New York, NY.

Progression of histologic damage in recurrent HCV appears to occur at an accelerated rate in allograft livers. HCV reinfection of the allograft occurs frequently, and it is feared that with increasing time from transplantation (LT), many patients will ultimately develop cirrhosis.

Aim: In order to better predict patient outcome and indications for treatment, we sought to establish a timeline for the progression of fibrosis in HCV patients developing cirrhosis post-LT.

Methods: Using the RMTI and pathology databases, all HCV patients with documented histologic recurrence up until 4/99 were identified. Those who had serial liver biopsies and chronic hepatitis (CH) with either stage 3 or stage 4 fibrosis were studied. Using current CH nomenclature, these biopsies were blindly staged (0 = no fibrosis, 1 = portal fibrosis, 2 = fibrous septa, 3 = transition to cirrhosis, 4 = cirrhosis) and graded (1 = mild, 2 = moderate, 3 = severe lobular activity) by a liver pathologist.

Results: HCV was the indication for LT in 468 patients, with 231 (49%) having documented histologic recurrence. Forty-two (18%) had stage 3–4. After excluding patients with concurrent vascular/biliary complications or cellular/ductopenic rejection, 30 patients (mean age 47.4 yrs, 16 males) were studied. Recurrent HCV infection was diagnosed on biopsies an average of 10.5 months post-LT in these patients. Progression from initial biopsy-proven diagnosis of hepatitis to stage 2 took 17.1 months (n = 8, range 2–55 months, though in 4 patients within 4 months), from stage 2 to 3 fibrosis, 27.5 months (n = 9, range 10–43), and from stage 3 to 4 fibrosis, 12 months (n = 7, range 1.5–16). Twelve patients progressed from initial biopsy-proven diagnosis of hepatitis to stage 3 on consecutive biopsies (mean 27.3 months, range 7–58), while 5 others progressed to stage 4 (mean 24.8 months, range 11–51). The average inflammatory activity was moderate to severe (grade 2.6/3) throughout all stages. Patients reaching stage 3–4 (n = 18) not requiring re-LT had mean PT 13.1 seconds, total bilirubin 2.6 mg/dL, serum albumin 3.4 g/dL, alkaline phosphatase 296 IU/L ALT 120 IU/L and AST 142 IU/L. At the first clinical evidence of portal hypertension, PT was normal with only minor abnormalities in serum bilirubin and albumin. Thirteen of 16 (81%) HCV patients progressing to stage 2–3 within 2 years of LT ultimately developed portal hypertension and/or required re-LT.

Conclusions: HCV patients who develop cirrhosis post-LT typically have early reinfection of their allograft with significant inflammatory activity. The development of stage 2–3 within 2 years of LT may be predictive for the ultimate development of portal hypertension and need for retransplantation. Hepatic synthetic function appears to be well preserved until patients develop signs of portal hypertension.

Role of Body Composition and Resting Energy Expenditures in Fatigue among Patients with Chronic Hepatitis C. N. Lau[1,2], K. Gardilla[2], S. Sigal[1,2], and D.P. Kotler[2]. [1]Division of Liver Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY; and [2]Division of Gastroenterology and Gastrointestinal Immunology, Department of Medicine, Columbia University/St. Luke's-Roosevelt Hospital, New York, NY.

Fatigue is a commonly reported symptom among patients with chronic hepatitis C (HCV) infection.

Aim: To assess fatigue using the Fatigue Impact Scale (FIS) and to correlate fatigue with body composition, exercise tolerance, and resting energy expenditure.

Method: Twenty-seven (27) patients with stable, non-cirrhotic chronic hepatitis C (9F, 18M) with mean age 45 years (range 28–55) were evaluated. Patients who were active alcoholics or receiving treatment with interferon were excluded. Patients rated their fatigue level using a self-reporting questionnaire that evaluated 3 dimensions: physical, cognitive and psychosocial. Body composition measurements (BCM) were made by bioelectrical impedance (BIA). Resting energy expenditure (REE) was measured by indirect calorimetry. A sub-maximal exercise test was performed using a modified bicycle test to estimate aerobic capacity.

Results: Total fatigue score, as assessed by the FIS, was associated with depletion of weight ($p = 0.04$) and body cell mass (BCM, $p = 0.007$). Patients who rated fatigue high, especially along the physical dimension, did well on the exercise bicycle test ($p = 0.012$). The predicted REE was calculated according to the Harris-Benedict equation. There was no difference found between the measured REE by indirect calorimetry and the predicted REE, indicating that the patients were normo-metabolic. Aminotransferase levels and REE did not correlate with fatigue. Patients scored highest in fatigue along the psychosocial dimension. Women scored higher fatigue levels along every dimension compared with men.

Conclusion: Subjective fatigue is associated with nutritional depletion as assessed by decreased weight and BCM, but not by objective evidence of impaired exercise capacity. This finding indicates that subjective fatigue is a poor predictor of physical capacity.

Inadequacy of Non-invasive Assessment in Detecting Significant Inflammation in Patients Undergoing Liver Transplantation for Chronic Hepatitis B. S.H. Sigal[1,2], A.D. Min[1], T.D. Schiano[1], M. Ye[3], K.B. Hussain[1], S.N. Thung[3], C.M. Miller[4], and H.C. Bodenheimer[1]. [1]Division of Liver Diseases, Department of Medicine, and Departments of [3]Pathology and [4]Surgery, Mount Sinai School of Medicine, New York, NY; and [2]Division of Gastroenterology and Gastrointestinal Immunology, Department of Medicine, Columbia University/St. Luke's-Roosevelt Hospital, New York, NY.

Recent reports indicate that lamivudine improves liver function in patients with decompensated cirrhosis associated with chronic hepatitis B (HBV). Theoretically, only patients with significant inflammation would benefit from such therapy.

Aim: To assess the activity of inflammation in liver explants from patients undergoing liver transplantation for chronic HBV, and the sensitivity of the biochemical and serologic assessment in detecting moderate-to-severe inflammation.

Methods: Liver chemistries, serologies (HBeAg, HBV DNA by liquid hybridization assay) and liver size (% predicted liver volume) of patients undergoing liver transplantation for chronic HBV from 1994 to 1999 were correlated with inflammatory activity in the liver explants. Pediatric patients and those with recent alcohol use, fulminant or subfulminant disease, portal vein thrombosis, hepatocellular carcinoma requiring pre-transplant treatment and concurrent HCV and HDV infection were excluded. Patients with recent use of anti-viral therapy were also excluded.

Results: 34 patients were available for review (29 male, 5 female). Mean age was 52.8 years (30–71), and 10 (29.4%) were Asian. Thirteen (38%) livers had minimal or mild inflammatory activity, while 21 (62%) had moderate or severe inflammation. The severity of inflammatory activity of those with minimal/mild vs. moderate/severe activity could not be predicted by ALT level (64.9 ± 12.9 vs. 63.9 ± 7.0 U/L), HBeAg+ status (5/12 vs. 5/16), ethnicity (3/13 vs. 6/21) or liver volume (70 ± 5 vs. 63 ± 4% predicted) ($p = \text{NS}$). Low but detectable HBV DNA levels (5.0 to 48.5 pg/mL) were more commonly present in patients with moderate/severe activity (7/19 vs. 1/12; $p = 0.04$). However, 12/23 (52%) patients with undetectable HBV DNA had moderate/severe inflammatory activity.

Conclusions: Moderate/severe inflammatory activity is present in 62% of patients undergoing liver transplantation for chronic HBV. Histologic inflammatory activity in patients with end-stage chronic hepatitis B is poorly predicted by biochemical, serologic or molecular markers of liver injury or viral replication.

Interferon alfa-2b and Ribavirin in Patients with Resistant Chronic Hepatitis C. A.D. Min[1], J.L. Jones[1], E. Lebovics[2], I.M. Jacobson[3], F.M. Klion[1], I.S. Goldman[4], S. Esposito[5], J.M. Geders[6], H. Tobias[7], and H.C. Bodenheimer[1]. [1]Division of Liver Diseases, Department of Medicine, Mount Sinai School of Medicine, New York, NY; [2]New York Medical College, New York, NY; [3]Cornell University Medical College, New York, NY; [4]North Shore University Hospital, Manhasset, NY; [5]New York Hospital, New York, NY; [6]Methodist Hospital, Brooklyn, NY; and [7]NYU School of Medicine, New York, NY.

The combination of interferon (IFN) and ribavirin has efficacy in previously untreated patients with hepatitis C or those relapsed after IFN alone. However, the effect of increased dose of IFN in combination with ribavirin is not known in resistant chronic hepatitis C.

Aim: Thus, this study was to evaluate the effect of an increased dose of IFN in combination with ribavirin on the efficacy of treating patients with chronic hepatitis C without sustained response to prior IFN therapy.

Methods: We randomized 159 patients with chronic hepatitis C to receive either 3 or 5 MU of IFN alfa-2b three times/week and ribavirin (1000–1200 mg/day) for 12 months, and followed them for an additional 6 months. Subjects were HCV RNA positive in spite of prior IFN therapy. Treatment was stopped at 6 months for subjects with less than a 90% reduction in viral load from the baseline. All subjects had liver biopsy within 2 years prior to study entry. Full follow-up data are available on 126 subjects. There were 100 nonresponders (NR) and 26 relapsers (R) to prior IFN therapy. Serum HCV RNA levels were measured using a quantitative PCR assay at baseline, 6; and 12 months of treatment and after 6 months post-treatment. Sixty-seven (53%) subjects were randomized to receive 3 MU IFN and 59 (47%) to 5 MU IFN.

Results: The mean age of the subjects was 47 years (range 28 – 68) and 91 (72%) were male. One-hundred-eight (86%) had genotype 1. Nineteen (15%) had cirrhosis on pre-study biopsy. The data at 12 months of treatment and at 6 months after the end of treatment are summarized in the Table.

At end of therapy	R (n=26)	NR (n=100)	3 MU (n=67)	5 MU (n=59)
HCV RNA (–)	13 (50%)	26 (26%)	18 (27%)	20 (34%)
HCV RNA (+)	13 (50%)	74 (74%)	49 (73%)	39 (66%)
At 6 months F/U	R (n=26)	NR (n=100)	3 MU (n=67)	5 MU (n=59)
HCV RNA (–)	9 (35%)	16 (16%)	11 (16%)	14 (24%)
HCV RNA (+)	17 (65%)	84 (84%)	56 (84%)	45 (76%)

There was a statistically significant difference in virologic response between the R and NR groups after 12 months of treatment (p = 0.034), but not after 6 months of follow-up (p = 0.065). There was no difference between subjects randomized to receive 3 MU and 5 MU of IFN alfa-2b, both at 12 months (p = 0.51) and at 6-month follow-up (p = 0.42). Fourteen of 39 (36%) subjects with (–) HCV RNA at 12 months subsequently had (+) HCV RNA at 6-month follow-up. Of those 14, ten (71%) were NRs to prior IFN monotherapy.

Conclusions: Although there was a significant difference in virologic response between relapsers and nonresponders at the end of 12-month therapy of combination treatment, there was no statistical difference in sustained response at the 6-month follow-up. When used in combination with ribavirin, 5 MU of IFN alfa-2b did not enhance the response rate compared with 3 MU.

Medical Oncology

Gastric Carcinoma at Elmhurst Hospital Center (EHC), 1990–1996. S.Khanwani[1] and A. Lyman[2]. [1]Housestaff, Mount Sinai School of Medicine and [2]Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Cancer of the stomach remains the second most common cause of cancer-related death in the world. The incidence is highest in East Asia, South America, and Eastern Europe. Gastric carcinoma is primarily a disease of the middle-aged and elderly; the proportion of patients ≤40 years of age has varied from 6 – 8%. However, a study done at an urban public hospital found that 15% of cases were in patients ≤ 40 years; young patients were more likely to be black.

Aim: A study was conducted at EHC, which has an ethnically diverse population with a large proportion of foreign-born patients, to examine the demographic, clinical and pathologic features of patients with gastric carcinoma.

Methods: From the Tumor Registry a list was obtained of all patients diagnosed from 1990 – 1996, and charts were reviewed. Odds ratios were calculated and chi-square analyses were performed using EpiInfo. One hundred and two patients had been diagnosed with gastric carcinoma; 90 charts (88%) were located and reviewed. The male:female ratio was 2:1. Thirty-five patients (39%) were Hispanic, 29 (32%) were Asian, 19 (21%) were white and 7 (8%) were black. Ten patients (11%) were # 40 years; comparing these patients with older patients, clinical staging was as follows: localized: 0 ([0%] vs. 16 [20%]), regional: 4 (40% vs. 18 [22.5%]), distant metastases: 6 ([60%] vs. 29 [36.3%]), unknown: 0 ([0%] vs. 17 [21.3%]). The odds ratio of males having local/regional disease as compared to distant/unknown was 2.54, which approached statistical significance ([95% confidence interval = 0.89,7.41], chi-square = 3.76, p = 0.053); corresponding odds ratio for Asians vs. Hispanics was 3.14 (95% confidence interval = 1.00, 10.02; chi-square = 4.92. p = 0.027). Epigastric pain was the presenting complaint in 54 patients (60%); 48 cases (54%) had proximal lesions.

Conclusions: Young patients accounted for a higher proportion of patients than is generally found; they were all Asian or Hispanic, and were more likely to have advanced disease. A substantial proportion of patients had proximal lesions; males may be more likely to be diagnosed at an earlier stage. Additional study is indicated to further define the risk in younger and foreign-born patients; physicians should have a high index of suspicion when treating patients from areas of high incidence.

Breast Carcinoma at Elmhurst Hospital Center (EHC). N. Adya[1] and A. Lyman[2]. [1]Housestaff, Mount Sinai School of Medicine (Elmhurst) Internal Medicine Residency Program and [2]Faculty, Ambulatory Care, Elmhurst Hospital Center, Elmhurst, NY.

Breast cancer is the most common life-threatening malignancy in North American women; mortality differences by race are known to exist.

Aim: To study the demographic characteristics of women with breast cancer in Elmhurst Hospital Center.

Methods: This is a retrospective cohort study of breast cancer patients with newly diagnosed breast cancer from January 1995 to December 1996. The patient list was obtained from the hospital tumor registry. Sixty-four patients were randomly selected from 114 patients, and hospital and tumor registry records were reviewed.

Results: The most common age category was 50!64 years (50%). Racial distribution: Caucasian 12 (18.75%), African American 12 (18.75%), Hispanic 19 (29.68%), East Asian 6 (9.37%), South Asian 5 (7.81%), Other 3 (4.68%) and not in chart 7 (10.93%). Family history of breast cancer: positive in 5 (7.81%), negative in 37 (57.81%), and not documented in 22 (34.37%). Menopausal status: postmenopausal 20 (31.25%), premenopausal 15 (23.43%), unknown 29 (45.31%) and late menopause 4 (6.25%). Early menarche was present in 10 (15.62%) and not documented in 30 (46.87%). Late age at first pregnancy: present in 9 (14.06%) including nulliparous, not documented in 26 (40.62%). Parity: nulliparous 4 (6.25%), one-two 12 (18.75%), three-four 13 (20.31%), five or more 6 (9.37%) and not documented in 29 (45.31%). History of benign breast disease: present in 1 (1.56%) and unknown in 57 (89.06%). History of radiation exposure: negative in one patient (1.56%) and unknown in 63 (98.43%). Oral contraceptive use: present in 1 (1.56%) and not documented in 63 (98.43%). Hormone replacement therapy: not documented in 61 (95.31%) and negative in 3 (4.68%). Estrogen receptor/progesterone receptor (ER/PR) status: +/+ in 20 (31.25%), +/- in 7 (10.93%), -/+ in 1 (1.56%), -/- in 7 (10.93%) and unknown in 29 (45.31%). Of 20 postmenopausal patients, ER and PR were positive in 11 (55%) and 7 (35%) respectively. Of 15 premenopausal patients, ER and PR were positive in 2 (10%) each. Grading: well differentiated in 3 (4.68%), moderately differentiated 15 (23.43%), poorly differentiated 10 (15.62%), undifferentiated 2 (3.12%) and unknown 34 (53.12%). Histology: carcinoma in situ (CIS) 3 (4.68%); infiltrating- ductal 41 (64.06%), lobular 5 (7.81%), ductal /lobular 3 (4.68%), adeno 2 (3.12%) and others 4 (6.25%). Staging: 0: 8 (12.5%), 1: 16 (25%), 2A: 7 (10.93%), 2B:9 (14%), 3A: 7(10.93%), 4: 1 (1.56%) and unknown:13 (20.31%). Comparing stage 0-4 at time of diagnosis, there was no significant difference between these data and data for 1992. Majority presented with lump- 25 (39.06%); 16 (25%) were self-reported. Screening mammogram diagnosed 8 (12.50%) patients; 57.81% patients were uninsured.

Conclusions: The most common presentation at diagnosis was a self-reported breast lump (25%); 12.5% were diagnosed by mammogram; stages 0, 1, 2 constitute 62.5%; a majority of the patients were uninsured, which could contribute to late presentation at diagnosis. Patients at EHC are not being diagnosed at an earlier stage than was found a few years earlier. Improved availability of screening mammography to this population might considerably improve outcome. Better documentation in hospital charts would facilitate future research.

Identification of PLZF Transcriptional Targets by Expression Profiling. M. McConnell and J. Licht. Derald H. Ruttenberg Cancer Center, Mount Sinai School of Medicine, New York, NY.

PLZF, a zinc finger transcription factor, is one of several fusion partners for the retinoic acid receptor alpha gene that is rearranged in acute promyelocytic leukemia. This rearrangement has been shown to disrupt normal cellular retinoid response pathways and presumably also disrupts PLZF pathways, although these latter pathways have not been established. The identification of genes altered by PLZF expression is the first step in deciphering these pathways. In order to find these genes, a tetracycline-regulated PLZF-expressor cell line was developed. At several time points after expression of PLZF was induced, mRNA was isolated and used to query a cDNA array (Research Genetics, Huntsville, AL). A temporal expression profile of genes both up- and down-regulated by PLZF was derived and confirmed by Northern blot. The validity of the Genefilter system, the list of identified genes, and their putative roles in growth suppression and tumorigenesis will be discussed.

Investigation of MMTV-like LTR in Human Breast Cancer. Y. Wang, J.F. Holland, and B.G.T. Pogo. Department of Medicine, Division of Medical Oncology, Mount Sinai School of Medicine, New York, NY.

The mouse mammary tumor virus (MMTV) has been regarded as a potential model for human breast cancer (BC). We have previously reported that a 660 bp MMTV-like env gene sequence was present in about 38% human BC, but not in the normal breast and normal tissues. We also found that 66% of the positive samples expressed this gene. The 3N long terminal repeats (LTR) sequence of the MMTV plays a very important role in mouse mammary tumorigenesis, since it contains several important elements, such as enhancers, promoters, glucocorticoid responsive element (GRE) and an open reading frame (ORF) for potential superantigen. These all have critical functions during the MMTV infection. Therefore, we have focused our research on LTR identification and expression. By using PCR, cloning and sequencing, a 630 bp fragment was first amplified from 32 human BC and breast cancer cell lines. It showed over 90% homology to MMTV LTR, but very low homology to any other known sequences in the genebank. Using an extra-long PCR and a nested PCR, a longer 1.2 Kb sequence was detected, and complete ORF and GRE elements have been identified. The results from the preliminary experiments also indicated that the LTR gene is expressed in BC. This human MMTV-like LTR has been cloned into a bacterial and a mammalian expression vectors to be used for detection in human tissues and functional assays. The results obtained from this research will help researchers understand the molecular mechanism(s) of human breast carcinogenesis, and identify new genetic markers possibly useful for diagnosis, prognosis and therapy.

Effect of Trehalose on Cell Kill Effects of Anticancer Agents or Hyperthermia against Human Tumor Cell Lines. L-T. Song, T. Ohnuma, and J.F. Holland. Division of Medical Oncology, Mount Sinai School of Medicine, New York, NY.

Trehalose is a non-reducing disaccharide found in organisms as diverse as insects, bacteria, fungi and algae, but absent from mammals. In these organisms trehalose serves not only as an energy source but also as a protectant against damage imposed by physical/chemical stresses such as poor nutrition, heat, dehydration, and exposure to hyperosmotic shock or to heavy metals. Thus, among insects and plants living in desert or subzero temperature, trehalose acts as an important anti-desiccant and anti-freezing substance. Trehalose has been successfully utilized as a storage solution for cells and organs for transplantation.

Aim: In view of the unique protective characteristics of trehalose on the host under stress, we attempted to determine whether trehalose plays a role on cell kill effects of anticancer agents or hyperthermia against human tumor cells, with a goal of eventually expressing a trehalose gene in host cells.

Methods: We examined the effect of trehalose on three human tumor cell lines using MTT assay on day 3 after adding the compound to culture medium.

Results: Increasing concentrations of trehalose in culture medium resulted in progressive inhibition of cell growth of Daudi lymphoma, HEp-2 laryngeal cancer and MOLT-3 ALL cells due to hypertonicity. Among the 3 cell lines, HEp-2 cells were able to tolerate the highest concentration of trehalose. Next, we examined the ability to support cell growth in media with decreasing glucose concentrations supplemented with increasing trehalose concentrations, making the media essentially isotonic. We observed that medium containing 0.007M glucose supported cell growth as efficiently as the original medium which contained 0.011M glucose. In the presence of 0.007M glucose, trehalose concentrations up to 0.04M supported optimal HEp-2 cell growth. In the presence of 0.004M – 0.04M of trehalose, cell kill effects of 0.3 μg/mL doxorubicin or 0.5 μg/mL vincristine on HEp-2 cells were essentially identical to those of no-trehalose control. At the trehalose concentration of 0.04M, doxorubicin concentration-cell kill curves overlapped with those with no-trehalose control. We also exposed HEp-2 and Daudi cells at 42°C for up to 3 hrs or at 0°C for up to 4 days with or without trehalose, and compared the cell kill effects. Presence of trehalose had no effects on hyperthermia- or hypothermia-induced cell kill effects.

Conclusions: Our study failed to show that trehalose, which had modulating effects in prokaryotes and lower animal forms, had any protective effects on human tumor cell lines when exposed to anticancer agents or to high or low temperatures under experimental conditions employed.

Study of Reovirus-Induced Cytopathic Effect (CPE) and Ras Protein in Human Tumor Cell Lines. L-T. Song[1], Irwin Gelman[2], J.F. Holland[1], and T. Ohnuma[1]. [1]Division of Medical Oncology and [2]Department of Microbiology, Mount Sinai School of Medicine, New York, NY.

Lee and his colleagues recently reported that reovirus selectively kills cells with an activated Ras pathway (Science 282:1332, 1998). Since Ras expression is a common phenomenon of a variety of human tumors, reovirus might serve as an effective anticancer agent. This information is of such importance that the relationship between the reovirus-induced CPE in a variety of human tumors and Ras expression needs to be thoroughly evaluated.

Aim: To examine the relationship between the degree of reovirus-induced CPE and the degree of Ras expression .

Methods: Reovirus serotype 3 was obtained from ATCC and maintained through serial infection of LLC-MK_2 cells. We examined reovirus-induced CPE, Ras protein amounts and viral RNA on 7 human tumor cell lines, including DND-1A melanoma, 2780 ovarian carcinoma, HEp-2 laryngeal squamous cell carcinoma, U87 glioblastoma and sublines, U87wt and U87 EGFR, and MCF-7 breast cancer. NIH/3T3 mouse embryo fibroblast and LLC-MK_2 monkey kidney cell lines were also included. CPE was determined by cellular rounding, granular appearance, degeneration, detachment from the floor, and eventual cell lysis and necrosis under microscopy. Amounts of Ras protein were assayed by Western blot using pan-Ras antibody. Four days after infection, viral RNA was detected by silver staining after PAGE.

Results:	Cell lines	CPE*	Ras*	Viral RNA§
	DND-1A	++	+	+
	2780	++	+	+
	HEp-2	+	+++	±
	U87	+	++	+
	U87wt	+++	+++	+
	U87 EGFR	++++	++++	+
	MCF-7	++++	++++	+
	NIH/3T3	–	+	–
	LLC-MK_2	+	+	+

(* graded from – to ++++, § presence + or absence – only)

Conclusions: All human tumor cell lines tested expressed Ras protein, and the intensity of protein expression appears to correlate with the CPE. In spite of identical very low expression of Ras in NIH/3T3 and LCC-MK_2 cells, reovirus produced CPE on LLC-MK_2 cells only. The nature of this difference is unknown, but the lack of CPE in NIH/3T3 cells may be related to PKR (dsRNA-activated protein kinase) phosphorylation after viral infection in this particular cell line.

Mass Spectrometric Identification of Intact Complexes of Etoposide with Albumin and Hemoglobin in Models and Serum. J. Roboz, L. Deng, and L. Ma. Division of Medical Oncology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Etoposide, a semisynthetic derivative of pedophyllotoxin, has been widely used in the treatment of several malignancies. The drug strongly binds to proteins, but little is known about the nature of the complexes.

Aim. Use electrospray ionization mass spectrometry to measure the molecular masses of intact complexes with albumin (Alb) and hemoglobin (Hb), to determine the number of bound molecules under different molar ratios and incubation times in models, spiked serum, and patient samples.

Methods: Etoposide and Alb or Hb were mixed (10:1 to 1:50 molar ratios) and incubated (0–24 hrs, 37°C). Human serum was spiked to therapeutic and toxic concentrations. Model samples were flow injected, spiked and patient serum samples were analyzed by LC/MS. Trace complexes were identified in the presence of large protein excesses by: (a) mass transformation scan-by-scan along the total ion current curve and (b) monitoring preselected multiply charged ions (m/z 1432, +47 charge and m/z 1463, +46 charge).

Results: With 2 – 10-fold excess Alb, the complex contained only 1 etoposide/Alb at all incubation times, molecular mass 67,326.3 ± 23.3 Da (n = 45), within 0.15% of the calculated value. Pickup of 1 etoposide was also detected in spiked serum at therapeutic doses. Increasing the quantity of etoposide led to complexes containing up to 9 etoposides, e.g., at 1:1 molar ratio, masses were detected corresponding to +2 (67,752 Da), +3 (68,236 Da), and +7 (70,502 Da) etoposides. Complexes with up to 8 etoposides/Hb were detected using 1:1 to 1:50 ratios, e.g., 15, 727 Da (+1 etoposide) and 18,189 Da (+5). All measured masses were within 0.01 to 0.5% of the calculated values. A representative patient sample contained Alb complexes with 1 and 3 attached etoposides, Hb complex with 1 etoposide, and 0.34 mmole/L free etoposide.

Conclusion. This methodology determines molecular masses of intact protein-drug complexes in the presence of large protein excess in serum. Knowledge of quantity and half-life of the complexes will lead to a better understanding of the observed influence of binding (e.g., adults vs. children) on the therapeutically important free drug fraction, and the possible monitoring of complexes for toxicity.

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Acylating Reactivity of the -CO-NH-CO- Moiety, a Structural Element of Some Antineoplastic and Teratogenic Antiepileptic Agents. Weisz[1], J. Roboz[1], I. Wolf[2], L. Deng[1], and J.G. Bekesi[1]. [1]Division of Medical Oncology, Department of Medicine, and [2]Department of Biochemistry, Mount Sinai School of Medicine, New York, NY.

While investigating the chemical reactivity of the 3-(bromoacetylamino)-benzoylurea, a new anticancer compound synthesized in our laboratory, we have found evidence that, in addition to the expected alkylating activity of the C-Br bond, acylating activity also appeared due to the presence of the diacylamine, -CO-NH-CO-, moiety.

Aim: To investigate the acylation reactions of cyclic diacylamines, cyclic acylureas and open-chain acylureas with the NH_2 and OH groups of nucleophiles.

Methods: The following diacylamine-containing compounds were investigated: (a) Cyclic diacylamines: succinimide, glutarimide, phthalimide; (b) Cyclic acylurea: dihydrouracil; (c) Open-chain acylureas: N-benzoyl-N'-phenethylurea, 3-(bromo-acetamino)-benzoylurea, phenylacethylurea. The compounds were reacted with: (a) 50- to 100-fold excess (weight) methanol or ethanol at 25 to 78°C for 0.5 to 3 hr; the reactions were catalyzed by NaHCO or K_2CO_3 ; (b) butylamine, phenethylamine, putrescine or N,N-dimethyl-ethylenediamine (molar equivalents) in water at room temperature for 1 to 24 hr. The reaction products were analyzed either after purification, e.g., succinimide-phenethylamine, or in the crude reaction mixture, e.g., phenylacetylurea-methanol. Molecular masses (protonated molecules) were determined by electrospray ionization mass spectrometry. When authentic compounds were available, identities were also confirmed by TLC or HPLC.

Results: The following reaction products were detected and characterized:

(a) From cyclic diacylamines: succinamidic acid methyl ester, succinamidyl-putrescine, succinamidyl-phenethylamine, succinamidyl-N,N-dimethyl-ethylenediamine, glutaramidic acid ethyl ester, glutaramidyl-putrescine, phthalimidic acid methyl ester.

(b) From dihydrouracil: β-ureidopropionic acid ethyl ester, β-ureidopropionyl-putrescine, b-ureidopropionyl-butylamine.

(c) From open-chain acylureas: benzoic acid methyl ester, 3-(methoxy-acetamino)benzoic acid methyl ester, phenylacetic acid methyl ester.

Conclusions: Acylation capability was confirmed for all compounds studied. Because the -CO-NH-CO- moiety appears in the structure of some antineoplastic agents, e.g., aminogluthetimide, aminofide, and teratogenic antiepileptic agents, e.g., phensuximide, phenacemide, there is a possibility that acylation may play an important role in their biological activity.

Pulmonary

*** Pulmonary Complications in Cardiac Transplant Recipients.** R. Lenner., G.J. Schilero., M.L. Padilla., A. Gass, and A.S. Teirstein. Department of Medicine, Division of Pulmonary and Critical Care and Cardiology, Mount Sinai School of Medicine, New York, NY; and Bronx VA Medical Center, Bronx, NY.

Introduction: The incidence of pulmonary complications in heart transplant recipients has not been extensively studied. We report pulmonary complications in 159 consecutive adult orthotopic heart transplantations performed in 157 patients at our institution between 8/86 and 9/98.

Methods: Retrospective review of medical records.

Results: Forty-seven of 159 (29.9%) recipients suffered 81 pulmonary complications. Pneumonia was most common (27/159, 17.2%-18 bacterial, 4 viral, 5 fungal), followed by bronchitis (15/159, 9.4%), pleural effusion (10/159, 6.3%), pneumothorax (7/159, 4.4%), tracheostomy (7/159, 4.4%), and obstructive sleep apnea syndrome (6/159, 3.8%). All patients with late onset, community-acquired bacterial pneumonia presented with fever, cough and a new lobar infiltrate on the chest radiograph, and responded promptly to empiric antibiotics without undergoing invasive diagnostic work-up. In contrast, early onset, bacterial pneumonias were nosocomial in nature, and carried a 33.3% mortality rate. Patients whose pre-transplant skin tuberculin test was positive were more likely to develop pulmonary complications (62.5% vs. 26.8%), and this difference was statistically significant ($p = 0.007$). The 18 recipients who initially received FK-506 as opposed to cyclosporine tended to have fewer pulmonary infections (5.6% vs. 29.6%) and post-transplant malignancies (0% vs. 4.3%), but these differences did not reach statistical significance. Induction immunosuppression with OKT3 in 61 recipients was associated with a significantly higher rate of lung cancer and post-transplant lymphoproliferative disorder (8.1% vs. 0%). We found no association between the presence or absence of pulmonary complications and the patients' age, gender, underlying cardiac disease and smoking history. Pulmonary infections occurred with similar frequencies regardless of the CMV serology of the donor and the recipient. During a mean follow-up of 3.4 years (0 – 12), the mortality rate of 23.5% (37 patients) correlated significantly with a higher rate of pulmonary complications (56.7% vs. 24.1%) that directly contributed to mortality in 11 of 37 patients.

Conclusions: Pulmonary complications were common following heart transplantation occurring in 29.9% of recipients, and were attributed to pneumonia of primarily bacterial origin in one half of the cases. Late onset, community-acquired pneumonias had an excellent prognosis following empiric antibiotic therapy, and these patients may forego invasive diagnostic work-up. In contrast, early onset, bacterial pneumonias were nosocomial in nature and carried a high mortality rate. PPD positivity was a significant risk factor for pulmonary complications. Initial immunosuppression with FK-506 as opposed to cyclosporine may decrease infectious complications and post-transplant malignancies, while OKT3 induction therapy was associated with an increased incidence of lung cancer and post-transplant lymphoproliferative disorder.

Is the Incidence of Pleural Involvement in Sarcoidosis Underreported? A Chest CT-CXR Comparison. J.B. Szwarcberg, N. Glajchen, and A. Teirstein. Pulmonary and Critical Care Division and Radiology Department, Mount Sinai School of Medicine, New York, NY

Pleural involvement in sarcoidosis has been reported to be 5 – 10% by conventional thoracic radiology. It is associated with severe advance disease and greater multiorgan involvement. Over a 6-month period, 61 patients from the sarcoidosis service at the Mount Sinai Medical Center, New York, NY, were observed. A computed tomography (CT) scan and chest X-ray (CxR), where available, were included in the observations. CT scans were independently evaluated by a masked radiologist and compared to a simultaneous CxR for absence or presence of pleural involvement (thickening or effusion). Pleural changes were compared to pulmonary function tests (PFT's), which were scored (1 = mild, 2 = moderate, 3 = severe). Twenty-five (25) (41%) of the 61 patients had pleural involvement by CT criteria (20 thickening, 5 effusion); only 7 (11%) had pleural involvement by CxR criteria (4 effusion, 3 thickening). Patients with CT pleural involvement had more fibrosis (stage IV CT 75% vs. 25% $p = 0.008$), worse restrictive impairment (54 vs. 46%), and a lower DLCO (68 vs. 32% $p = 0.012$) on PFT's. One patient had a pleural effusion on CxR, which was not present on a subsequent CT performed after furosemide.

	CT+	CT–	TOT
CxR+	6	1	7
CxR–	19	35	54
TOT	25	36	61

CxR showed a sensitivity of 24% and a specificity of 97% for pleural involvement. The incidence of pleural involvement by CT scan in sarcoidosis was much higher than previously reported by conventional CxR. The presence of pleural involvement occurs in more advanced disease.

A Comparison Between the Frequency of Pneumothorax Complicating Transbronchial Lung Biopsy (TBLB) of the Upper and Lower Lobes.

M. Ismail, R. Theerthakarai, C. Anselmi, and M.A. Khan. St. Joseph's Hospital and Medical Center, Paterson, NJ; and Seton Hall University, School of Graduate Medical Education, South Orange, NJ.

Aim: The incidence of pneumothorax complicating TBLB is estimated to be 1–4%. Which lobe is more vulnerable to this complication has not been determined. Since the upper lobes are relatively more distended than the lower lobes due to a more negative surrounding pleural pressure, pneumothorax may be more frequent following TBLB in an upper lobe. To assess the validity of this hypothesis, we retrospectively reviewed our experience with 160 patients who underwent TBLB.

Methods: We reviewed the medical records of all patients who underwent bronchoscopy and TBLB at our institution during a twenty-month period. We excluded patients who underwent more than one-lobe biopsy as well as those in whom the biopsy site was not defined.

Results: A total of 160 patients (90 males, 70 females; age range from 22 to 94 years, mean age: 56.8 years) were studied. The number of biopsies ranged from 1–4. There were 49 patients with an upper lobe biopsy, 94 patients with a lower lobe biopsy, 12 with middle lobe and 5 with lingular biopsy. Only two patients developed pneumothorax following a lower lobe biopsy and none after an upper lobe biopsy.

Conclusion: There is no increase in the risk of pneumothorax following an upper lobe TBLB as compared to a lower lobe biopsy.

A Comparison of Drug-Resistant Tuberculosis in US-Born and Foreign-Born Patients in an Inner-City Community.

R. Theerthakarai, M. Ismail, C. Anselmi, and M.A. Khan. St. Joseph's Hospital and Medical Center, Paterson, NJ; and Seton Hall University, School of Graduate Medical Education, South Orange, NJ.

Aim: Comparatively high prevalence of drug-resistant tuberculosis (TB) is seen in foreign-born individuals. To assess the prevalence of drug-resistant TB in both the US-born and foreign-born patients in our community, we reviewed our experience over a four-year period.

Methods: We retrospectively analyzed the confirmed TB cases with culture positive disease from July, 1994 to June, 1998, at the Paterson Board of Health Chest Clinic. Two hundred and one (201) patients (108 US-born and 93 foreign-born; age range: 4 months – 93 years; mean age: 44; male: 108, female: 93) were found eligible for the study.

Results: The incidence of drug-resistance among the US-born and foreign-born was 8% (9 patients) and 26% (24 patients) respectively ($p = 0.005$). Multi-drug resistance was found in 1 (1%) in US-born and 7 (8%) in foreign-born patients. The resistance to individual drugs is as follows:

	INH	RIF	PZA	EMB	SM
US-born	4 (4%)	0 (0%)	0 (0%)	3 (3%)	3 (3%)
Foreign-born	18 (19%)	4 (4%)	3 (3%)	3 (3%)	10 (11%)

Conclusions: These results indicate that the rates of resistance to all first-line drugs except ethambutol were higher in foreign-born than in US-born patients. The incidence of single and multi-drug resistance was also higher in foreign-born than in US-born patients.

Pilot Study of IV Prostacycline in the Treatment of Pulmonary Hypertension Secondary to Pulmonary Sarcoidosis.

M. Padilla[1], R. Lenner[1], S. Kushwaha[2], M. Poon[2], and A.Teirstein[1]. [1]Division of Pulmonary and Critical Care Medicine, and [2]Division of Cardiology, Mount Sinai School of Medicine, New York, NY.

Pulmonary hypertension (PH) is a devastating result of chronic lung disease and usually indicates approaching death. Lung and heart-lung transplantation have been successful in some patients. Recently, both primary pulmonary hypertension (PPH) and secondary PH have been treated medically with prostaglandin inhibitors.

Aim: To compare IV prostacycline in the treatment of patients with marked PH due to sarcoidosis and patients with PPH.

Material and Methods: Three patients from the sarcoidosis service of the Mount Sinai Medical Center, New York, NY with Stage IV chest radiographs and PH unresponsive to steroid and antimalarial medications (pulmonary arterial pressure [PAP] range 66–95/20–40 mm Hg, mean (m) 40–60 mm Hg) and 6 patients with PPH (PAP 70–105/25–57 mm Hg, m. 40–70 mm Hg) were treated with IV prostacycline (PC). Following initiation of PC, the patients were evaluated biweekly for any changes in clinical response.

Results: The 3 patients with sarcoidosis had no clinical response to treatment with PC. These 3 died 2 to 7 months after beginning PC therapy. In contrast, only one of 6 patients with PPH expired; the other 5 clinically improved 3 to 26 months after beginning PC treatment.

Conclusion: In this small pilot series, PC did not confer the same improved prognosis for patients with PH due to sarcoidosis as it did for those patients with PPH. Further studies of patients with PH and sarcoidosis, and PH secondary to other diseases may give insight into the apparent lack of benefit from prostacycline in patients with PH due to sarcoidosis.

The Effect of Inflammation on Airway Smooth Muscle Stretch-Induced Relaxation.

R. Carrillo-Bislick, G.S. Skloot, D. Chandy, A. Enriquez, A. Gadgil, and E.N. Schachter. Mount Sinai School of Medicine, New York, NY.

Airway hyperresponsiveness in asthma may be a problem of limited smooth muscle relaxation with inspiration (Skloot et al. JCI 1995; 96:2393). We have previously studied the response of stretch-induced relaxation (SIR) in guinea pig trachea (AJRCCM, 1998; 157:A515), in order to evaluate the role of mediators in this response. In the current study, we evaluated the role of allergic inflammation in SIR. Guinea pigs were sensitized using 3 repeated intraperitoneal injections (0.5 mL of a 6 mg/mL solution of ovalbumin [OA]) given over a one-week period. On day 21, the guinea pigs were challenged with an aerosol of 2.5% OA. A control group of unsensitized animals, followed concurrently, received a sham challenge of double distilled water. Both groups were sacrificed 24 hours after challenge. Guinea pig tracheal rings were then suspended in physiologic buffer and maintained at a baseline tension of 2 g. Individual rings were then stretched by applying tensions 2.5, 5, 10 or 15 g. After equilibration, the tissues were washed and reset to 2 g tension. Carbachol (10^{-4}M) was added and the tissues allowed to reach maximal constriction. The response to stretch was again studied. A total of 5 sensitized and 3 control animals have been studied to date. The inflammatory response in sensitized animals was confirmed histologically by the presence of extensive infiltration of eosinophils into the mucosal epithelium (not seen in controls). The SIR response in inflamed tissue was not significantly different from that in uninflamed tissue, either in the absence or presence of carbachol. These initial data suggest that SIR in guinea pig trachea is not influenced by the inflammatory response elicited by a single challenge with OA in sensitized animals. Repeated antigen challenge may cause airway remodeling; its effect on SIR remains to be determined.

Differences Between the Bronchoprotective Effect of Fast and Slow Deep Inspirations.

D. Chandy, R. Carrillo-Bislick, E.N. Schachter, and G.S. Skloot. Mount Sinai School of Medicine, New York, NY.

Deep inspiration (DI) protects against pharmacologically induced bronchoconstriction in healthy subjects (HS) but not in asthmatics. A possible mechanism in HS is that DI stretches airway smooth muscle and breaks crossbridges, while in asthmatics, inflammation impairs this ability. We hypothesized that in HS this effect is related to inspiratory velocity, i.e., a fast (F) DI is more bronchoprotective than a slow (S) DI. We studied 10 HS (mean FEV1 % pred ± SE = 98 ± 3), screened on day 1 by standard methacholine (Mch) challenge ($PC20 > 75$ mg/mL). On day 2, subjects performed 3 FVC maneuvers and then underwent modified Mch challenge without DIs (0 DI); only partial forced expirations were done after each dose. The threshold dose (DT), defined by symptoms and/or partial $FEV1/FVC < 0.65$, was followed by 3 FVC maneuvers. All subjects had >20% reduction in FEV1 from baseline, a prerequisite for further study. On days 3 and 4, the protocol was identical to that of day 2, except that immediately prior to DT, subjects performed either an FDI or an SDI respectively (mean maximal inspiratory flow rate [L/s] 5.58 vs. 1.15, $p < 0.01$; mean inspired volume (l) 3.02 vs. 3.23, p = NS). The % reduction (mean ± SE) in FEV1 and FVC post-DT (compared to baseline) on days 2–4 is shown.

		% Reduction	
		FEV1	FVC
Day 2	0 DI	34 ± 4	23 ± 3
Day 3	SDI	31 ± 5	19 ± 4
Day 4	FDI	20 ± 3*	12±3†

Significant differences were seen for FEV1 (*FDI vs. SDI, $p = 0.018$) and FVC (†FDI vs. SDI, $p = 0.009$). These results suggest that a fast DI is more bronchoprotective than a slow DI in HS. We speculate that this may be due to enhanced breakage of crossbridges.

Histamine Bronchoprovocation Testing: Comparison of Methods. D. Grimm[1,2], D. Chandy[1,2], G. Schilero[1,2], and M. Lesser[1,2]. [1]Bronx VA Medical Center, Bronx, NY, and [2]Departments of Medicine, Mount Sinai School of Medicine, New York, NY.

Previously, we demonstrated by use of a logarithmic/manual method (LMM) that most subjects with tetraplegia exhibited airway hyperreactivity (AHR) in response to aerosolized histamine. However, this method may be associated with inhalation of increased amounts of histamine as compared to more standard protocols.

Aim: The objective of this study was to compare our method with two standardized methods (2 minute tidal breathing [TBM] and dosimeter [DM]) in the determination of AHR in persons with tetraplegia.

Methods: Nine subjects with tetraplegia were randomized to perform 3 histamine challenges by the different methods, which were administered at least one week apart. Both standard methods used doubling concentrations of histamine, whereas our method used logarithmic concentration increments. For the TBM, aerosol was generated by a Salter 8900 nebulizer driven by air (50 psi) at a flow rate of 8 L/min with an output of 0.35 μL/min. Particle size ranged from 1.6 – 3.4 μm and was delivered via a face mask for 2 min. For the DM, aerosol was generated by a DeVilbiss dosimeter 646 nebulized attached to a Rosenthal-French dosimeter driven by compressed air (20 psi), for a duration of 1.42 sec, producing an output of 0.31 mL/min. Particle size ranged from 2.37 – 2.75 μm. Five breath-actuated maximal inhalations were performed for each incremental dose. For the LMM, aerosol generation, flow rate and particle size were the same as the TBM. Nebulization was done by manual occlusion of a thumbport and 5 maximal inhalations were performed.

Results: No significant differences for mean baseline spirometry or mean LnPC20 values were found between the 3 bronchoprovocation challenge methods (TBM LnPC20 = 0.32 ± 1.31; DM LnPC20 = 0.21 ± 1.15; LMM lnPC20 = 0.59 ± 1.05 mg/mL). Significant correlations were found for all comparisons among the methods: TBM vs. LMM $r = 0.95$, $p < 0.001$; DM vs. LMM $r = 0.81$, $p < 0.009$; TBM vs. DM $r = 0.87$, $p < 0.005$.

Conclusion: The LMM for bronchoprovocation can be used as another reliable method for performing histamine challenge studies.

Pharmacologic Characterization of Organic Dusts from the Tobacco Industry. E.N. Schachter, E. Zuskin, N. Rienzi, S. Goswami, and H. Singh. Mount Sinai School of Medicine, New York, NY.

In a recent study we evaluated workers exposed to tobacco dust in a cigarette manufacturing plant. An excess of respiratory symptoms and lung function abnormalities was noted. Water soluble extracts from dusts collected from tobacco leaves (TDE) were prepared as a 1:10 w/v solution. Dose-related contractions of nonsensitized, guinea pig trachea (GPT) were demonstrated using these extracts. TDE was added to the GPT's in 1/2 log dose increments. Response was measured as a percent of maximal carbachol contraction. The effects of mediator-modifying drugs, as well as an angiotensin converting enzyme inhibitor (captopril), a calcium channel blocking agent (TMB8) and capsaicin were tested. Atropine inhibited TDE over the entire range of doses tested. Pyrilamine, indomethacin, acivicin, NDGA, and BPB (a phospholipase A2 inhibitor) had variable effects on TDE induced constriction. Pre-treatment with capsaicin depleted irritant nerves of bronchoconstricting mediators, and resulted in a modest reduction of TDE induced constriction. Additionally, we fractionated the crude TDE by molecular weight (< 10 Kd and > 10 Kd) and by lipid content. Most of the contractile effect of TDE was found in the low molecular weight delipidated fraction of the TDE. The lipid-containing fraction was not found to have any constrictor activity. We conclude that TDE exerts a non-immunologic constrictor effect on guinea pig tracheal muscle. The mechanism of this contractile effect is complex and capable of being modulated by a wide variety of mediator-modifying agents. Anticholinergic agents in particular appear to exert a profound blocking effect on this extract. Partitioning studies of the extract indicate that the activity is concentrated in the low molecular weight, non-lipid fraction of the extract.

Very Elderly Critically Ill Patients: What Is a Good Outcome? D.M. Nierman[1], L.M. Cannon[1], C. B. Schechter[2], and D.E. Meier[3]. The Departments of [1]Medicine, [2]Community Medicine and [2]Geriatrics, Mount Sinai School of Medicine, New York, NY.

Purpose: Decisions regarding the value of critical care for very elderly patients (> 85 years) depend on the desired outcomes. However, what these patients and their surrogates consider to be an acceptable outcome is unknown.

Subjects and Methods: Telephone interviews were conducted with very elderly patients or their surrogates within 1 to 2 years following hospitalization and intensive care at a tertiary, academic medical center. The interview included the Mount Sinai Care Center Survey, Spitzer's Quality of Life Index, and Patrick's Perceived Quality of Life (PQOL) Scale.

Results: Of 222 very elderly patients, 171 (77%) survived the hospitalization. A total of 146 (66%) interviews were conducted. Eighty-eight percent (88%) of patients living at home would have been willing to repeat the ICU experience again, as would 87% of surrogates of patients living at home, 78% of surrogates of patients living in skilled nursing facilities (SNFs), 96% of surrogates of patients who died in the hospital, and 59% of surrogates of patients who died after hospital discharge. Patients living in SNFs had significantly worse function than patients living at home as assessed by Spitzer's Quality of Life Index; however, their Patrick's PQOL scores were comparable.

Conclusions: Independent of the outcome, respondents to these interviews felt that the ICU admission was worthwhile. For hospital survivors, patient-perceived QOL was acceptable independent of level of function or place of residence. The definition of a successful ICU outcome for this patient population deserves reexamination.

Psychiatry

Hemispheric Specialization for Selective Attention. S. Chokron, A.M. Brickman, T-C. Wei, and M.S. Buchsbaum. Neuroscience PET Laboratory, Department of Psychiatry, Mount Sinai School of Medicine, New York, NY.

The pulvinar, a major association nucleus of the thalamus, may mediate the selective filtering of non-pertinent information. Previous imaging studies have suggested a role of the pulvinar in selective attention, but have not examined visual hemifields separately. New studies are needed to test for a hemispheric asymmetry occurring at the sub-cortical level. The current project provides evidence for the suitability of a new neuropsychological task to demonstrate hemifield differences in selective attention. This selection requires a filtering process that would ensure an amplification of the target and/or an attenuation of the background information.

Aim: To test for a hemispheric asymmetry in selective visual attention.

Methods: Twenty (20) normal subjects performed a letter detection task in which the attentional demand was varied. The letter to be detected could appear alone as a big stimulus or small and surrounded by flankers. In order to test for hemispheric specialization in the filtering processes, the stimuli were displayed horizontally, either in the left or in the right hemifield, or vertically, either above or below the fixation point. Subjects were signaled as to whether they were correct or incorrect, by presenting a blue background for incorrect trials. The task was carried out without this feedback with the conditions in a counterbalanced order.

Results: A significant interaction between the type of stimulus (alone or surrounded by flankers) and the hemifield of presentation (left or right) was found only in the condition where subjects were presented stimuli horizontally without any feedback. In this condition, reaction times (RTs) were shorter in the left hemifield rather than in the right one for single large stimuli, while on the contrary for stimuli surrounded by flankers, RTs were shorter in the right hemifield rather than in the left one.

Conclusions: The present findings suggest a right hemifield (left hemisphere) advantage for visual analysis of complex visual displays and suggest that the current task will be useful in fMRI imaging studies of selective attention and pulvinar function.

Radiology

Magnetic Resonance Imaging Expands the Detection of Musculoskeletal Sarcoidosis. S. Moore[1], A. Teirstein[2], and L. DePalo[2]. [1]Department of Radiology and [2]Division of Pulmonary and Critical Care Medicine, Mount Sinai School of Medicine, New York, NY.

Reviews of the clinical manifestations of sarcoidosis stress the frequency of intrathoracic disease and a few common extrathoracic sites such as eyes, skin, liver, and lymph nodes. Although musculoskeletal symptoms are among the patient's most common complaints, there has been little interest in the extent of bone, tendon, synovial and muscle involvement beyond the well-recognized "punched out" lesions of the small bones of the hands and feet, usually confirmed by standard radiographs. MR imaging optimizes soft tissue contrast and is sensitive for evaluation of marrow infiltration and subtle bony lesions occult on plain films. Accordingly, MR scanning promises to enlarge the visualization and characterization of musculoskeletal manifestations of sarcoidosis.

Aim: To assess the value of MR imaging in musculoskeletal sarcoidosis.

Materials and Methods: Ten patients with sarcoidosis proven by tissue biopsy and/or Kveim test, who presented with symptoms suggesting musculoskeletal sarcoidosis, were evaluated. Standard plain films, bone scan and MRI on 1.5 Tesla magnet were performed, focusing on the symptomatic area.

Results: Six patients demonstrated lesions detected with MRI which were underestimated, or not detected, on plain films. Manifestations included paraosseous and marrow granulomatous infiltration, tenosynovitis, and myositis. In some cases, bone scans aided in localizing lesions prior to MRI scanning.

Conclusion: These preliminary data strongly suggest that musculoskeletal sarcoidosis is common and more extensive than previously detected, and may account for the high frequency of somatic complaints in sarcoidosis patients. MR imaging accurately assesses soft tissue involvement, as well as marrow infiltration in the axial skeleton, which may be radiographically silent. Further studies of MR imaging in patients with various presentations of sarcoidosis are indicated.

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Rheumatology

Occult Active Giant Cell Aortitis Requiring Surgical Repair. Y.J. Chang, L.D. Kerr, S. Flagg, K. Dowling, J. Weintraub, R. Sathyanarayanan, H. Spiera, and J. Fallon. Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Aortitis complicated by aneurysm or dissection may be a more prevalent complication of giant cell arteritis (GCA) than has been previously recognized.

A retrospective chart review of 1069 aortic repairs or replacements performed at the Mount Sinai Medical Center uncovered 19 patients (n = 19) whose tissue demonstrated active GCA. Of these 19 patients, only one had a prior diagnosis of GCA by temporal biopsy. None had a recent history of symptoms referable to the temporal arteries. Cardiovascular symptoms consisting of dyspnea on exertion (12/19), angina (6/19) and orthopnea (4/19) predominated. Physical signs consisted of a new murmur in 14/19, with aortic insufficiency confirmed in 9/19. Erythrocyte sedimentation rates were not obtained.

At surgery, 17/19 had thoracic aortic aneurysms, 2 with dissection; 6/19 had aneurysms of both the thoracic and abdominal aortas; and 2/19 had aneurysms of the abdominal aorta alone. Of the nine aortic valves replaced, none had valvulitis. All patients were discharged without further treatment or follow-up.

These data document that clinically occult active GCA necessitating aortic repair occurs, perhaps with increasing incidence. Since GCA is a systemic rather than a localized disease, earlier identification of these patients and the use of immunosuppressive therapy may prevent this catastrophic complication.

Monoclonal (Type 1) Cryoglobulinemia: Long-Term Follow-up of 8 Patients. Y.J. Chang, S Glabman, S Dickman, R.G. Phelps, and P.D. Gorevic. Departments of Pathology and Medicine, Mount Sinai School of Medicine, New York, NY.

Patients with monoclonal (Type I) cryoglobulinemia comprise only ~6% of a recent large series of patients with cryoglobulinemia. Although ~6% of IgG myeloma proteins and ~10% of macroglobulins are cryoglobulins, in as many as ~30% of patients no underlying plasma cell dyscrasia is apparent, even after detailed clinical and pathologic evaluations. We retrospectively collected data over 13 years (1986!1999) on 8 patients (5 men and 3 women; mean age 52 years) with type I ("essential") cryoglobulinemia, who did not have any underlying hematological malignancy or connective tissue disorder; 6 had IgGk paraproteins, one IgM, and one a biclonal (IgMÿ/IgGÿ) gammopathy. Mean duration from the initial manifestations until the diagnosis of cryoglobulinemia was 28 months, and mean duration of follow-up after diagnosis of cryoglobulinemia was 8 years. Initial manifestations were: cutaneous (6); musculoskeletal (3); renal (2); and neurological (1). Mucocutaneous manifestations included macules/papules (4); petechiae (3); leg ulcers (3); livedoid skin lesions (5); purpura (5); acrocyanosis (4); bluing of ear helices (3), nasal erosions (1); and Raynaud's phenomenon (2). Symptoms were reproduced by ice cube test challenge in one patient. Musculoskeletal manifestations were frank arthritis (2), arthralgias (4); and myalgias (2). Neurological symptoms were paresthesias (5) and foot drop (1). Fifty percent (50%) of patients developed clinical or biochemical evidence of renal disease, including renal insufficiency (3), proteinuria (4), or nephritic syndrome (1). One patient had chronic irritative corneal deposits solubilized by the application of warm compresses to the lids.

Cryoglobulin concentration at diagnosis varied from 0.8 – 11 mg/mL, with a mean viscosity of 1.6 on routine testing; of the 7 IgG-containing cryoproteins, 4 were IgG1 and one each IgG2, IgG3 and IgG4; direct N-terminal sequence analysis of heavy and light chain bands immunoblotted from gels did not reveal selective VL or VH subgroup usage. No patient had positive serology for hepatitis B or C (HCV) virus initially, and no cryoprecipitate was positive for HCV by RT-PCR; ANA and Rheumatoid Factor were negative. Only one patient had low C3 and C4 on repeated testing. Leukocytoclastic vasculitis was apparent in skin (5/5), renal (1/2) and nerve (1/1) biopsies, with 40% of skin, both renal, and the nerve biopsy also showing prominent intravascular inclusions. One renal biopsy showed mesangiocapillary glomerulonephritis which recurred in an allograft following transplantation, during which the patient became infected by HCV; both renal biopsies had eosinophilic PAS-positive hyaline inclusions with crystalline ultrastructure.

Therapies were: glucocorticosteroids (100%); immunosuppressive therapy (75%); plasmapheresis (62%) and intravenous immunoglobulin (IVIG) (37%). Over a 7-year period of follow-up, one patient has continued to require IVIG, and two others have remained clinically stable off all medication. There were 2 deaths, one from abdominal sepsis and the other from complication of bone marrow transplant. Type I cryoglobulinemia is clinically, biochemically, and serologically distinct from the more common Type II and Type III cryoglobulinemias and is only rarely associated with HCV infection; patients may not evolve to defined plasma cell dyscrasias or known lymphoproliferative disorders, even after long periods of follow-up. Disease pathogenesis involves both inflammatory and thrombotic mechanisms, and in some instances can be reproduced by direct cold challenge testing.

Renal Transplantation in Scleroderma. Y.J. Chang and H. Spiera. Division of Rheumatology, Department of Medicine, Mount Sinai School of Medicine, New York, NY.

Although the outcome of renal transplantation in patients with SLE has been studied, there are few reports about the outcome of patients with PSS who have undergone renal transplantation. We retrospectively collected data from the United Network for Organ Sharing Scientific Renal Transplant Registry (UNOS) over a 10-year period. Eighty-six (86) PSS patients who underwent renal transplantation were identified. Of these 86 patients, 70% were women, 86% were Caucasians, with the mean age at transplantation 50.4 years. The overall mortality was 24% of the patient group; 44% (38/86) of renal grafts failed. First through fifth year graft survival rates were 62%, 60%, 57%, 50% and 47%, respectively. The causes of graft failure could not be ascertained in 25 of 38 patients (64%). Among the known causes, 5 had acute rejection, 4 had chronic rejection, 2 had recurrence of scleroderma (criteria accepted by UNOS), and 1 each had infection and graft thrombosis.

Immunosuppressive regimens utilized in the PSS patients consisted of anti-lymphocyte globulin in at least 25%. Sixty percent (60%) received a combination of steroids, azathioprine and cyclosporine. The use of cyclosporine was neither associated with improvement of graft survival nor an increase in the rate of the graft failure. A comparison of graft survival of PSS patients with that of SLE patients who received renal transplantation revealed comparable graft survival at 1 and 5 years.

Based upon this data, renal transplantation is as effective a treatment for restoring renal function in PSS patients as it is in SLE patients. Those PSS patients whose renal function did not improve with ACE-inhibitor treatments after scleroderma renal crisis, should be considered transplant candidates. Although the data are incomplete, the use of cyclosporine may not confer the advantage of improving graft survival in PSS patients as compared to SLE patients.

Spinal Cord Research

Venous Vascular Function in Subjects with Spinal Cord Injury Compared to Sedentary and Active Controls. J. Wecht[1,2], J. Weir[4], A. Spungen[1-3], W. Bauman[1-3], and D. Grimm[1,2]. [1]Spinal Cord Damage Research Center and Medical Services, Bronx VA Medical Center, Bronx, NY; [2]Departments of Medicine and [3]Rehabilitation Medicine, Mount Sinai School of Medicine, New York, NY; and [4]University of Osteopathic Medicine and Health Sciences, Des Moines, IA.

Alterations in peripheral blood flow associated with spinal cord injury (SCI) are the result of both sympathetic denervation and the loss of an active muscle pump. Determining the contributions of autonomic denervation and the absence of orthostasis to alterations in peripheral circulation may have important clinical implications in persons with SCI.

Aim: To describe venous vascular function in subjects with SCI and in sedentary (S) and active (A) able-bodied controls.

Methods: Forty-eight (48) subjects were studied, 24 individuals with SCI, 12 S and 12 A. Venous vascular function was assessed by strain-gauge venous occlusion plethysmography.

Results: Venous vascular function is expressed as mean ± S.D and is presented (Table 1). Maximal venous distention (VDm) was significantly reduced in the SCI group compared with both S and A groups, and also in the S relative to the A group. Total venous outflow (VOt) was significantly lower in the SCI group than in the S and A groups and in the S versus the A group. Venous emptying rate (VEi) was significantly higher in the S and A groups compared to the SCI group. When expressed as an index of VDm however, VEi was significantly higher in the SCI group compared with the S and A groups. Finally, venous resistance (VR), an indirect estimate of venous compliance, was significantly higher in the S and A groups compared to the SCI group.

	SCI	Sedentary	Active	$p<0.05$
VDm %	0.31 ± 0.13	1.61 ± 0.76	2.1 ± 0.55	1,2,3
VOt % *sec	2.95 ± 1.3	39.0 ± 18.8	66.7 ± 45.2	1,2,3
VEr % /sec	12.2 ± 6.6	33.6 ± 19.2	44.1 ± 19.4	1,2
VEi %	39.3 ± 13	21.2 ± 8.9	21.2 ± 4.9	1,2
VR %	0.22 ± 0.12	0.75 ± 0.15	0.78 ± 0.20	1,2

1 = SCI vs. SED, 2 = SCI vs. ACT, 3 = SED vs. ACT

Conclusion: Regular orthostatic challenge and exercise may improve vascular compliance and peripheral circulation in individuals with SCI.

Surgery

Splenic Artery Aneurysm in the 1990s. S.P. Dave, E.D. Reis, A. Hossain, P.J. Taub, M.D. Kerstein, and L.H. Hollier. Department of Surgery, Mount Sinai School of Medicine, New York, NY.

Splenic artery aneurysms (SAA), although rare, are the most common aneurysms of visceral arteries. Like most aneurysms, SAA are usually asymptomatic and diagnosed incidentally; however, rupture can cause serious morbidity or death. Pregnancy and portal hypertension have been associated with an increased risk of SAA, but the mechanisms are poorly understood. Advances in non-invasive diagnosis and minimally invasive therapy have generated controversy regarding the optimal management of SAA.

Aim: Assess risk factors, management, and outcome of a recent series of patients with SAA.

Methods: A retrospective review performed at our institution identified nine patients with a diagnosis of SAA in the last 12 years (1988 to 1999). Demographics, clinical features, treatment, and outcome were analyzed.

Results: The mean patient age was 60.5 (range: 31 to 81) years. Six were women, three were men. Associated conditions were essential hypertension (6), smoking history (4), portal hypertension (3), diabetes (1), intracranial aneurysm (1), and polyarteritis nodosa (1). At the time of diagnosis, 6 SAA were asymptomatic (incidental findings), 2 were ruptured, and 1 was causing abdominal pain. Diagnosis was made by angiography (2), computed tomography (3), ultrasonography (3), and exploratory laparotomy (1). Aneurysm size varied from 2 to 9 cm. One patient had multiple aneurysms in the splenic artery, and the patient with polyarteritis nodosa had micro-aneurysms or dilations in other visceral arteries and iliac arteries. Six patients underwent open surgery (4, elective; 2, emergency [ruptures]); 5 with splenectomy. One patient had coil embolization; and 2 (with aneurysms <3 cm) had no intervention. Three patients died postoperatively, at 2 days (ruptured intracranial aneurysm), 4 days (myocardial infarction), and 9 months (overwhelming sepsis).

Conclusions: In this series, incidence of portal hypertension was a common factor related to SAA, perhaps because our institution has a large number of liver transplant patients. Despite predominance in women, no aneurysms were noted during pregnancy. Open surgical treatment often required splenectomy. Postoperative mortality correlated with presence of severe co-morbidity.

Thrombosis Research

Leukocytes Transfer Tissue Factor to Platelets during Thrombus Formation. U. Rauch[1], D. Bonderman[1], B. Bohrmann[3], J.T. Fallon[2], J.J. Badimon[2], M. Riederer[3], and Y. Nemerson[1]. [1]Division of Thrombosis Research, Department of Medicine and [2]Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY; and [3]F. Hoffmann La. Roche Ltd., Basel, Switzerland.

Arterial thrombosis is known to occur after a vessel is damaged and blood is exposed to vessel-wall tissue factor (TF). Recent observations demonstrate that TF is also present in the circulating blood. Thrombi generated on collagen-coated slides by human blood stain heavily for TF. TF in thrombi appears mostly on membrane vesicles that are attached to platelets pointing to cells as the main source of blood-borne TF. TF-positive polymorphonuclear leukocytes can be isolated from the circulation and are also detectable in thrombi. Leukocytes coincubated with platelets generate more procoagulant activity than either cell alone.

Aims: To investigate whether human leukocytes transfer TF to platelets during thrombus formation. To identify the membrane adhesion molecules that mediate the TF transfer. To determine whether blocking antibodies to the identified membrane adhesion proteins inhibit the TF transfer from leukocytes to platelets.

Methods: A human monocytic cell line (THP-1) was induced with TNF to produce TF. THP-1 cells were mixed with washed human platelets and perfused over a collagen-coated slide at a shear rate of 500 sec^{-1}. Alternatively, a platelet carpet was deposited on the slide and then perfused with THP-1 cells. TF-transfer to platelets was identified by immunohistochemistry and flow cytometry. Immunoelectron microscopy was used to co-localize TF and leukocyte adhesion molecules in thrombi. The effect of antibodies (anti-CD15 and anti-TF) on TF transfer was tested by flow cytometry.

Results: THP-1 cells transferred TF to the platelets in both perfusion systems. TF was co-localized with CD15 on membrane vesicles that attached to platelet aggregates. Leukocyte-derived vesicles were assessed for surface proteins: 60% were positive for CD15, 14% for CD18, and 45% for TF. TF transfer to platelets was reduced 50% to 65% by blocking antibodies against anti-CD15. Monoclonal antibodies to TF inhibited the TF transfer to platelets by approximately 75–85%.

Conclusions: Leukocytes transfer TF-positive vesicles to platelets, which render the platelets capable of propagating coagulation. TF-transfer is mediated by the interaction of CD15 on leukocyte-derived membranes with P-selectin on platelets. The inhibition of TF transfer by CD15 antagonism may represent a therapeutic strategy for prevention of arterial thrombosis.

Queens Hospital Center

Lymphocytic Interstitial Pneumonitis in an HIV-Infected Adult. R. Ahmed, A. Goswami, N. Adhami, M. Hanif, V. Azueta, R. Ayinla, and J. Fleischman. Departments of Medicine and Pathology, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Lymphocytic interstitial pneumonitis (LIP) was first described in 1966, and until 1980 most cases were associated with dysgammaglobulinemic states. In 1983, the disease was reported among Haitian adults and children with other manifestations of HIV. In 1985, the CDC identified histologically proven LIP as an AIDS-defining diagnosis in children under 13 years of age unless the serological tests for HIV are negative. In 1991, LIP was reported in 30–50% of children with pulmonary complication of AIDS. In contrast, LIP has only been described in 3% of HIV-infected patient who present with a pulmonary opportunistic infection. A recent review of pulmonary complications of AIDS noted that LIP has a tendency to occur earlier in the course of HIV infection prior to the occurrence of many other opportunistic infections. Because of the possibility in some patients of resolution of LIP either with or without retroviral therapy, there are no clear guidelines for treatment, although some authorities describe improvement with corticosteroid treatment.

Case Report: A 34-year-old male from Congo (an AIDS endemic area), a U.S. resident for 4 years, presented with chronic cough, hemoptysis and a 20-pound weight loss over three years. He was sexually promiscuous. On clinical examination, the patient had low grade fever and bilateral basal rales. His complete blood count and chemistry were remarkable for anemia. LDH was 180 IU/liter. Arterial blood gas on room air revealed — pH 7.46, pCO2 36.6, pO2 72.8, with an increased A-a gradient of 32 torr. CD4 count was markedly reduced (65) with elevation of viral load (55,000 copies). HIV serology was positive. Chest X-ray showed bilateral reticulonodular infiltration mostly in the mid and lower lung zones but sparing the apical areas. Transbronchial biopsy of the right lower lobe revealed hyperplasia of pneumocytes and interstitial infiltrate of lymphocytes, plasma cells and histiocytes without granuloma. Stains for acid fast bacilli, fungi and *Pneumocystis carinii* pneumonia were negative. These findings were consistent with LIP. Because of symptomatic dyspnea and troublesome cough, corticosteroid therapy was initiated. Four weeks later, significant improvement was noted on follow-up chest X-ray. Marked improvement in gas exchange (ABG pH 7.4, pCO2 40, pO2 95 and A-a gradient 4 torr) was noted after six weeks of therapy.

Discussion: This patient demonstrated typical radiographic and histologic features of LIP. LIP has not previously been reported as a first manifestation of AIDS in an adult. Since prior reports noted LIP to occur early in the course of HIV disease, our patient is also unique in that he presented with an advanced stage of HIV disease. His improvement with corticosteroid therapy, radiographically and physiologically, is noteworthy, particularly since there are no clear-cut guidelines for treatment of this disorder in the AIDS patient. Further studies are required to better define this noninfectious pulmonary complication of AIDS.

Cocaine-Induced Sickle Cell Crisis in a Patient with Sickle Cell Disease. A. Aziz[1], M. Undavia[1], A. Husain[2], T. Santucci Jr.[1], and F. Rosner[2]. [1]Department of Medicine, Jamaica Hospital, Jamaica, NY, and [2]Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Painful crises in patients with sickle cell disease are often precipitated by infections, hypoxia, metabolic derangements or dehydration. We report a case of painful sickle cell crisis in a 28-year-old woman with sickle cell disease induced by cocaine abuse.

Case Report: A 28-year-old African American woman with sickle cell disease presented to the emergency room complaining of generalized body aches especially in the back and the extremities. She denied fever, cough, diarrhea or urinary symptoms. She has had episodes of vaso-occlusive crisis about twice a year in association with recreational cocaine abuse.

The patient was alert and oriented but in moderate distress from pain. The only significant physical findings were pallor and icterus. The hematocrit was 27.8%, leukocyte count 17,300/mm^3 with a normal differential, reticulocyte count 12.5%, Hgb S 91%, and serum lactate dehydrogenase 327 IU/L (normal range 100–200 IU/L). Chest roentgenograph and urinalysis were normal. Urine toxicology screen revealed the presence of cocaine. The patient was treated with intravenous fluids and analgesics. Her previous hospitalization for painful crisis was also preceded by cocaine use confirmed by a positive urinary toxicology screen.

Conclusion: A fatal combination of cocaine overdose and a cocaine-induced sickle cell crisis was previously reported in a 38-year-old woman (1). In our patient, the presence of cocaine in the urine on two separate occasions during painful crises strongly suggests the association between cocaine and sickle cell crisis. The mechanism of the crisis may be related to cocaine-induced vasoconstriction.

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Guillain-Barré Syndrome and Babesiosis: A Case Report. N. Bharany, H. Dhingra, F. Rosner, and D. Brennessel. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Acute ascending paralysis in adults has many etiologies. Guillain-Barré syndrome (GBS) is the most common cause of acute ascending paralysis in adults and represents a demyelinating process of the peripheral nervous system. Abundant evidence points to the role of the immune system, although viruses (cytomegalo and Epstein-Barr), lymphoma, systemic lupus erythematosus, Rocky Mountain spotted fever and influenza vaccine have been reported in association with GBS.

Case Report: We report a case of GBS associated with babesiosis. The patient initially presented with fever, malaise, rigors and chills. Ring forms of babesia species were found on the peripheral blood smear. Indirect immunofluorescence was positive for *Babesia microti*. The patient responded well to quinine and clindamycin.

Three weeks later the patient developed gait disturbance, severe-to-moderate degree of weakness in distal and proximal muscles, respectively, in both upper and lower limbs, and areflexia. Both superficial and deep sensations were minimally impaired. Cerebrospinal fluid analysis revealed glucose 52 mg/dL, protein 91 mg/dL, and 7 leukocytes, mainly lymphocytes. Nerve conduction studies showed the evidence of a diffuse sensory-motor polyneuropathy with mixed features of axonal and demyelination pattern. Clinical diagnosis of GBS was made.

One day later, he developed respiratory weakness which required mechanical ventilation. The patient was treated with plasmapheresis and intravenous immunoglobulins for two weeks. Muscle power gradually improved, and he was weaned off the ventilator after three weeks. Twelve weeks later he had completely recovered.

Fatal Necrotizing Pancreatitis and Fascitis in a Patient with Pulmonary Sarcoidosis (Stage III). A. Briones, G. Shidham, C. Saha, S. Chokhavatia, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Symptomatic gastrointestinal involvement in sarcoidosis is infrequent and severe pancreatic involvement is rare.

Case Study: A 31-year-old African American woman, a social alcohol drinker, treated intermittently with steroids for pulmonary sarcoidosis (stage III), was hospitalized for severe breathlessness. She was treated with intravenous steroids and improved. On the fourth hospital day, she developed severe persistent epigastric pain, with increased serum amylase (293 U/L) and lipase (314 U/L) levels. The patient's condition deteriorated rapidly. The severity of the pancreatitis and the increased risk for mortality were evidenced by (1) Ranson's criteria [four risk factors, namely: leukocytosis (26,500/mm^3), hypoxemia (P_{02} of 33 mmHg), high serum LDH (437 IU/L), and hypoalbuminemia (3.1 g/dL)], and (2) the Acute Physiology and Chronic Health Evaluation (APACHE-II) scoring system (score of 12 points). She developed methicillin-resistant *Staphylococcus aureus* pneumonia, empyema, and eventually respiratory failure necessitating endotracheal intubation and mechanical ventilation. Dynamic computed tomography (CT) scan of the abdomen revealed multiple pancreatic pseudocysts and ascites (Grade E on the CT grading system of Balthazar and Ranson). These findings prompted surgical exploration which revealed a hemorrhagic and necrotic pancreas with necrotic posterior fascia requiring extensive debridement. Despite aggressive medical and surgical management, the patient failed to improve and eventually died on the fiftieth hospital day. Acute pancreatitis in patients with sarcoidosis is usually clinically benign and responds to steroid therapy. Our patient developed a severe fatal pancreatitis, despite aggressive medical and surgical treatment.

Lumbosacral Radiculopathy due to Rapid Fluid Retention and Acute Renal Failure. B. Chen and N. Paddu. Department of Physical Medicine and Rehabilitation, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Introduction: Lumbosacral radiculopathy is a common clinical entity with many causes. To our knowledge, fluid retention as a cause for this disease has not been described.

Case Study: A 45-year-old man with major depression was hospitalized due to sedative Unisom (doxylamine) overdose. He was unresponsive with severe metabolic acidosis, impaired renal function and a markedly increased serum creatine kinase (CK) level (129,708 U/L). The patient was intubated and received a large amount of IV fluids as part of the treatment for rhabdomyolysis. His renal function deteriorated quickly, with total urine output of 1,880 mL, in spite of an intake of 19,928 mL in the first 3 days. As a result, dependent edema occurred, particularly in both thighs and left lumbosacral area (due to the supine position). When the patient became alert, he complained of pain, numbness and weakness of the left lower extremity but had no lower back pain. He was unable to move that limb. Electrodiagnostic studies (EMG) demonstrated left lumbosacral radiculopathy and sciatic nerve compressive neuropathy with an extensive denervation process. A non-significant diffuse central disc bulge was noted on a magnetic resonance imaging (MRI) scan. A computed tomography (CT) scan of the lower extremity demonstrated extensive fluid collection bilaterally along the iliac crest down to the knees. When edema subsided with hemodialysis, the symptoms gradually improved.

Conclusion: This patient developed radiculopathy and sciatic nerve compression due to rapid fluid retention and improper positioning. Recognition of this condition, proper positioning of the patient during the comatose state, and careful management of fluid intake may prevent this complication.

Metastatic Disease to the Patella from a Large Cell Carcinoma of the Lung: Case Report and Review of the Literature. J. Daly and I. Ashley. Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: We cared for a 45-year-old man with large cell carcinoma of the lung who complained of pain in the right knee and was found to have metastatic carcinoma to the patella. The patella is an extremely rare site of metastatic disease from cancer.

Method: The 32 reported cases of metastatic cancer to the patella were reviewed with analysis of the common primary sites of cancer, the prognosis, and response to therapy.

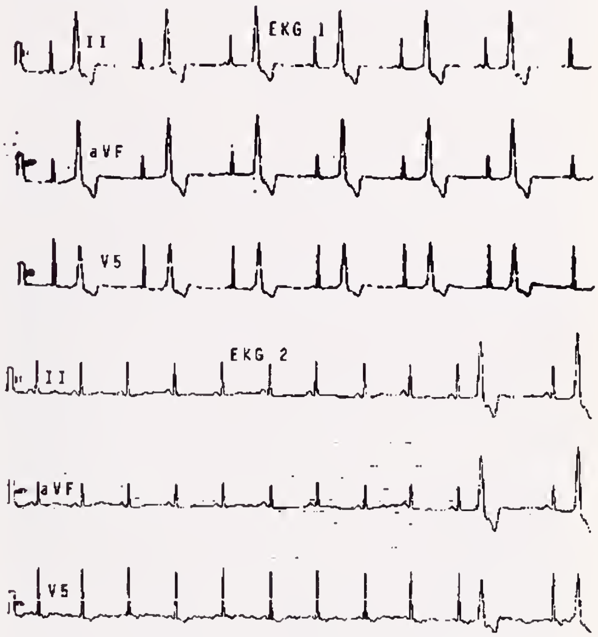
Results: The most common primary cancer site was the lung (9 cases), followed by breast cancer (5 cases), lymphoma (3 cases), and 2 cases each of melanoma, kidney, and esophagus. Other primary sites and histologies were varied. Histology included squamous cell carcinoma, adenocarcinoma and small cell carcinoma. Treatment included patellectomy, radiotherapy and systemic treatments such as chemotherapy or hormone therapy. The ultimate prognosis depended on the responsiveness of the primary cancer to systemic treatment rather than local treatment (i.e., radiotherapy or patellectomy). The mean survival time was 7.5 months.

Conclusion: Metastatic disease to the patella should be considered in patients with cancer who develop significant pain in the knee. The prognosis is poor and various treatments are only palliative.

Bigeminy and Its Treatment in the Heroin Abstinence Syndrome. A.K. Goswami, Y. Khan, R. Ahmed, M. Morgan, and E. Johnson. Department of Emergency Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Abstinence syndrome from heroin is generally mild since the street drug is usually impure. Occasionally, however, the withdrawal may include a manifestation requiring immediate attention. We report a patient with heroin withdrawal who developed bigeminal rhythm, along with symptoms which responded to intravenous morphine. Different arrhythmias have been described in withdrawal from substances like alcohol etc., but our Medline search did not reveal bigeminy in heroin withdrawal.

Case Report: A 32-year-old black female, a heroin addict, came to the emergency department a few hours after stopping heroin sniffing. The patient gave a history of hypertension and diabetes type II and was taking Glucotrol, Procardia and methadone. She had not taken her medication for two days. The patient was asymptomatic with a pulse of 68 beats per minute, BP 186/112 mmHg, normal size pupils and no piloerection. The patient was given Procardia 10 mg and clonidine 0.1 mg for her hypertension. After four hours she started vomiting, became restless, the pupils became dilated, piloerection was noted, the pulse was 70 and BP 160/94. The patient was given another dose of clonidine 0.1 mg. She also complained of palpitation, chest pain and difficulty in breathing. EKG revealed bigeminal premature ventricular contractions. Two mg of morphine was given intravenously and within minutes her symptoms abated and the rhythm became predominantly sinus (Figs. 1 and 2).



Discussion: Opioid inhibits adenyl cyclase activity in the nucleus locus caeruleus and other centers in the central nervous system, resulting in decrease in cAMP levels. In an addict, there is progressive compensatory increase in adenyl cyclase levels, so that normal cAMP levels are eventually maintained. On withdrawal, since adenyl cyclase is no longer inhibited, cAMP activity and, therefore, noradrenergic activity is increased in these center resulting in withdrawal manifestations. This increased noradrenergic activity can be blocked by exogenous opioids, acting on opioid receptors or by clonidine acting on central presynaptic alpha 2 receptors. Clonidine has been extensively used for the withdrawal symptoms, as it is nonaddictive and less expensive. If opioid is selected, methadone is the drug of choice. Very rarely is it necessary to administer opioid acutely to treat opioid abstinence. Dysrhythmias, resulting from an excess catecholamine, as in our case, may represent such a situation.

Premature ventricular contractions (PVC) may occur in a variety of pathological and nonpathological states and as such are not an indication for treatment. However PVC of Lown class 3 and above may degenerate into ventricular tachycardia or ventricular fibrillation and need treatment in different clinical settings (1). Our case according to these criterion was of class 5 and hence needed prompt attention. In settings of ischemia, lidocaine can lessen or abolish PVCs and is recommended for Lown class 3 and above. In other situations beta blockers or calcium channel blockers may be more appropriate. Acutely administered opioid may be an appropriate treatment in PVCs of Lown class 3 and above in opioid withdrawal syndrome as exemplified by our case.

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Quinapril-Induced Pancreatitis. A. Goswami, T. Otrok, L.Kasturi, S. Chokhavatia, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and the Mount Sinai School of Medicine, New York, NY.

Introduction: Drugs are a relatively uncommon cause of pancreatitis in adult patients. There are very few reports of patients with pancreatitis-associated angiotensin converting enzyme (ACE) inhibitor therapy, such as captopril. We report an elderly woman with quinapril-induced pancreatitis.

Case Study: A 65-year-old nonalcoholic, white woman was hospitalized for severe upper abdominal pain radiating to the back, nausea and vomiting. A cholecystectomy for cholecystitis had been performed in 1974. Quinapril was started about eight months before this episode. Additional medications included pravastatin, glyburide, omeprazole, levothyroxine, risperidone and sertaline.

On admission, there was diffuse upper abdominal tenderness. The liver function tests were as follows: AST 29 U/L (2–40 U/L), ALT 22 U/L (2–50 U/L), total protein 5.1 g/dL (6.5–8.5 g/dL), albumin 2.0 g/dL (3.5–5.5 g/dL), total bilirubin 0.6 mg/dL (0–1.5 mg/dL), and conjugated bilirubin 0.1 mg/dL (0.1–0.4 mg/dL). The serum amylase was 5841 U/L (0–130 U/L), lipase 646 U/L (13–104 U/L) and triglyceride 274 mg/dL (52–97 mg/dL). On abdominal ultrasound, the common bile duct was normal with no stone. Computed tomography of the abdomen showed an enlarged pancreatic head and extensive peri-pancreatic infiltration with edema consistent with mild acute pancreatitis. All medications were discontinued. The patient gradually improved over the next eight days with resolution of the abdominal pain. The serum amylase decreased to 74 U/L and the lipase level to 34 U/L.

All medications, except quinapril, which was thought to be the cause of the acute pancreatitis in the absence of any other etiology, were restarted. At six-month follow-up, the patient had no further episode of pancreatitis.

Discussion and Conclusion: Definite proof that a drug causes pancreatitis requires that: (1) pancreatitis develop during treatment with the drug; (2) other likely causes of pancreatitis are not present; (3) pancreatitis resolves upon discontinuing the drug; and (4) pancreatitis usually recurs upon re-administration of the drug. Our patient met the first three criteria. We did not re-administer quinapril. Drug-induced or drug-related pancreatitis is remarkably uncommon, especially in view of the fact that there has been a dramatic increase in the number of new drugs during the last 25 years. A listing of drugs with definite association, probable association and possible association has been reported. Our patient's other drugs are not included in this listing. The relative rarity of drug-induced pancreatitis requires the gradual accumulation of information, by case reports such as ours.

Neuropsychological Assessment of Older Adults: Differentiation of Dementia from Normal Age-Related Decline. Bret S. Grube. Department of Psychiatry, Division of Psychology, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

One of the most difficult challenges for neuropsychological assessment is determining whether changes in cognitive functioning in older adults are normal age-related changes, or are indicative of a dementing process. This is especially true in borderline situations, in which there is decline in cognitive functioning that warrants clinical attention, but the decline is not significantly below that which is expected following normal age-related cognitive changes. In fact, a new nosology is developing to characterize these instances, and it consists of such categories as "Benign Senescent Forgetfulness" for those people less likely to become demented, and "Incipient Dementia" for those more likely to progress toward dementia. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) includes research criteria for "Mild Neurocognitive Disorder" that might apply in such borderline cases and which does not imply a particular prognosis. There is currently no easy way to determine whether somebody who is experiencing mild or moderate memory problems in older age will go on to develop severe problems associated with dementia (as in Alzheimer's Type), or whether these problems will remain static and subclinical (as in normal age-related decline), or even improve or remit (as when due to other problems such as depression, hypothyroidism, or another medical condition that may partially or fully remit). While standardized neuropsychological testing provides objective evidence of problems in memory and other areas of cognitive functioning (e.g., "executive," language), and scanning techniques such as functional magnetic resonance imaging (*f*MRI), positron-emission tomography (PET), and single photon emission computed tomography (SPECT) provide complementary evidence of brain functioning, other methods are available to help determine the extent to which these problems are progressive and may result in dementia. Repeat testing six months to one year following initial ("baseline") neuropsychological assessment can provide objective data pertinent to the rate of progression of cognitive decline; in addition, assessment in the form of careful history taking from the examinee and those who know the examinee well can also shed light on the rate of decline. In some cases, it is helpful to estimate earlier, "premorbid" levels of functioning in the absence of objective data collected at that time, and methods are available to accomplish this based on careful analysis of newly collected data and on prior psychosocial functioning and demographic information. There is also new normative information emerging on the nature of changes in cognitive functioning that are expected across the lifespan and in older age; these norms are essential when interpreting test data in this context. Refinement of assessment and diagnostic procedures is critical in light of recent advances in the pharmacological and rehabilitative treatments for dementia and other cognitive disorders, and in light of the aging of the population.

Prevalence of Thrombocytopenia in the Intensive Care Unit of a Municipal Hospital. A. Husain, R. Jamshidian, and I. Ashley. Department of Internal Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Study Objective: To identify the incidence and risk factors of thrombocytopenia in a community hospital intensive care unit (ICU).

Method: Charts of patients admitted to the ICU during a 12-month period (1998) were reviewed. Patients with platelet counts less than 100,000/mm^3 were selected for further assessment. This group was studied with respect to the lowest platelet count they had during the ICU stay, the length of ICU stay, and other associated risk factors. The clinical significance of thrombocytopenia was also assessed.

Results: Charts of 400 patients were studied, with 42 patients having platelet counts less than 100,000/mm^3.

The major underlying diagnoses leading to ICU admission in these 42 patients were delirium tremens (13), respiratory failure (7), cardiac arrest (6), cancer (6), AIDS (4), liver disease (3) and miscellaneous (3). Risk factors included alcoholism (15 patients), heparin use (9 cases), furosemide (7 cases), penicillin analogue use (6 cases), renal disease (6 cases), cardiac arrest (6 cases) and cancer (4 cases).

The lowest platelet count for the 42 patients is indicated in the Table.

Discussion and Conclusions: The incidence of significant thrombocytopenia in our ICU was 10%. Seventeen patients had platelet counts less than 50,000/mm^3. The majority of these patients had two or more risk factors. Thus, the severity of thrombocytopenia correlates with the number of risk factors. The major diagnoses among these patients were delirium tremens, respiratory failure, cancer, AIDS and liver disease. The significant risk factors identified were drugs (alcohol, furosemide, heparin, penicillins and cimetidine); disease states such as renal disease, cancer and sepsis; and clinical conditions requiring central lines and mechanical ventilation. (Heparin was not used to maintain patency of the central line, neither was subcutaneous heparin used for deep vein thrombosis prophylaxis.) A large number of patients had alcohol-related thrombocytopenia; none had less than 50,000 platelets. All, however, had good prognoses with subsequent normalization of platelet counts. The severity of thrombocytopenia was related to respiratory failure with subsequent intubation, the length of ICU stay and subsequent adverse outcome. Three patients had unexplained thrombocytopenia; all three had counts around 75,000/mm^3 with no subsequent morbidity, and all recovered soon after discharge from the ICU.

TABLE

Platelet Counts

Lowest Platelet Count per mm³	No. of Patients
0 – 10,999	4
11,000 – 20,999	1
21,000 – 30,999	6
31,000 – 40,999	2
41,000 – 50,999	5
51,000 – 100,000	24

***Pneumocystis carinii* Pneumonia as the First Presentation of HIV Infection in the Elderly.** V. Jedlovsvky and J. Fleischman. Department of Medicine, Mount Sinai Services Queen Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: The number of elderly patients first diagnosed with HIV infection at the time of presentation with an AIDS-related opportunistic infection has increased over the past several years. This increase has been observed in all categories of HIV transmission risk factors. From 1991 – 1996, a 53% increase in AIDS cases diagnosed in this manner has been reported in injection drug users, with a 94% increase in patients with heterosexual contact risk factors. This suggests a significant delay in the diagnosis of HIV infection and may lead to delayed administration of antiretroviral therapy as well as prophylactic therapy for opportunistic infection. It is also a missed opportunity for education and behavior modification to decrease the spread of HIV infection.

Method: We retrospectively reviewed records of all elderly patients (>50 years of age) admitted to a municipal New York city hospital over a three-year period with confirmed *Pneumocystis carinii* pneumonia. This age cutoff was utilized as the Centers for Diseases Control (CDC) invokes a minimum of 50 years of age for epidemiological studies on HIV infection in the elderly. The clinical presentation, hospital course and outcome were reviewed and compared with published data for younger age groups.

Results: The mean patient age was 57.9 ± 6.6 years. In 80% (8 of 10 cases), the diagnosis of HIV infection was made at presentation with *Pneumocystis carinii* pneumonia (PCP). The mean CD4 count was 34.2 ± 39.2/mm³ (1 – 117/mm³), indicating advanced AIDS. The clinical presentation of PCP was similar to that in younger patients. With prompt and appropriate therapy, including initiation of appropriate anti-PCP treatment on day 1 of hospitalization, a 70% survival rate for this hospitalization was achieved, similar to that reported in younger age groups.

Discussion: The diagnosis of HIV infection was not considered until presentation with PCP at an advanced stage of AIDS in 80% of these elderly patients, thus delaying initiation of HIV treatment and counseling. Possible factors contributing to a delay in diagnosis may include: (1) poor access to medical care, (2) a misperception that HIV is a disease of younger age groups, or (3) masking of HIV/AIDS symptoms by comorbid disease which was present in 60% of our patients. Early consideration of HIV infection in the elderly is important because of the increasing number of AIDS cases in this age group. Our study suggests that when the diagnosis of AIDS/PCP is considered in the elderly and appropriate therapy is begun, favorable outcomes can be achieved.

Community-Acquired Native Valve *Staphylococcus epidermidis* Endocarditis in a Patient with Cerebral Palsy. S. Karuvannur and D. Brennessel. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: We report a unique 37-year-old male with cerebral palsy who presented with *Staphylococcus epidermidis* native valve endocarditis. Although coagulase negative staphylococci are the most common cause of prosthetic valve endocarditis, native valve endocarditis occurs infrequently (1). Most reported patients had documented valvular abnormalities.

Case Report: A 37-year-old man with cerebral palsy was brought from his nursing home with complaints of lethargy, inability to swallow and poor appetite. The patient had cerebral palsy and a seizure disorder since birth. He had multiple admissions in the past for phenytoin toxicity and aspiration pneumonia, the last admission being in 1992.

There was no history of past surgery, allergies, smoking, alcohol or illicit drug use. He was receiving phenytoin 100 mg three times a day and clonozepam 1 mg twice a day. His family history was not contributory. Three days prior to hospitalization, the patient had an upper respiratory infection for which he was receiving erythromycin.

On physical examination, the patient was a young black man, uncommunicative, and lying in a curled fetal position. There was no pallor, icterus, petechia, splinter hemorrhages, Osler's nodes, Roth's spots or Janeway lesions. He had conjunctivitis. The blood pressure was 120/80 mmHg, heart rate 66 beats per minute, respiratory rate 18 per minute and temperature 91°F. Pupils were equal and reactive to light. There was no heart murmur or splenomegaly. Pulmonary, abdominal and rectal exams were unremarkable. Both lower limbs had contractures at the hips and knees, and he had a right wrist drop. He was nonverbal and had no meningeal signs.

The blood leucocyte count was 11,000/mm³ (3.4 – 10,000/mm³), hemoglobin 14.3 g/dL, hematocrit 43.6% (42 – 52%) and platelets 239,000/mm³ (150 – 450,000/mm³). His phenytoin level was 56 μ (10 – 20 μ/mL). Electrocardiogram showed sinus rhythm with prolonged QT interval (480 ms) and chest roentgenogram was within normal limits.

Because of hypothermia, the patient was treated with intravenous vancomycin and clindamycin pending cultures for presumed sepsis. Four sets of blood cultures drawn over a 24-hour period grew methicillin-resistant *S. epidermidis*. Vancomycin was continued; clindamycin was discontinued. A transthoracic echocardiogram was performed but did not reveal any vegetations. A transesophageal echocardiogram showed a 1.1 cm vegetation on the tricuspid valve, normal valvular anatomy and normal left ventricular function.

The patient received vancomycin for 30 days and remained normothermic since day two of hospitalization. Repeat blood cultures were negative. He remained symptom free thereafter and was discharged to his nursing home on the forty-first day of admission.

Discussion: Previously considered a contaminant, *S. epidermidis* and other coagulase negative staphylococci are nowadays leading causes of nosocomial infection (2). The rise in incidence is attributed to the wide use of medical devices such as vascular catheters, shunts, prosthetic valves and joints in the care of hospitalized and chronically ill patients. *S. epidermidis* infection associated with devices tends to produce "slime," an exopolysaccharide that mediates adherence of the organism to the smooth surface of the prosthetic device. In a biofilm environment, organisms that are highly sensitive *in vitro* become resistant *in vivo*. Our patient with *S. epidermidis* endocarditis of a normal tricuspid valve had no vascular or prosthetic device. He seems to have acquired the infection outside the hospital setting. Community acquired *S. epidermidis* native valve endocarditis has been reported before (2) but it is very rare. Usually the organism is susceptible to methicillin. In contrast, hospital acquired *S. epidermidis* endocarditis is more common on prosthetic valves and more often involves methicillin resistant strains. Combination therapy has been advocated in the presence of methicillin resistance. However, this patient responded well to treatment with vancomycin alone, probably because there was no vascular or valvular prosthesis.

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Review of Infective Endocarditis over an Eleven-Year Period at a Public Hospital. S. Karuvannur, D. Brennessel, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: We reviewed the predisposing factors, presenting signs and symptoms, time to diagnosis, bacteriology, echocardiographic findings, complications and outcome of patients with infective endocarditis. A retrospective analysis of 51 cases of endocarditis as defined by the criteria of Duke (1) was conducted for the period from January 1, 1987 to December 31, 1997.

Materials And Methods: Queens Hospital is a municipal hospital that serves a population of one million people in the Borough of Queens. On an average, there are 16,583 discharges per year, 56% of whom are female and 44% male. Of these patients, 59% are black, 17% Hispanic, 12% white, 5% Asians and others 9%.

Charts of 130 patients were reviewed. Only 51 cases met the Duke criteria for infective endocarditis. Reasons for retrospective disqualification were negative blood cultures with no other evidence of endocarditis, absence of vegetations in patients without other clinical criteria or resolution of symptoms without treatment. The following data were obtained: age, sex, race, pre-hospital duration of illness, coexisting disease, dental history, presenting complaints, complications, results of investigations, treatment and outcome.

Results: The mean age of the 51 cases was 38 with a range from 21–75 years. The incidence was higher in Blacks (82%) and in males, the ratio of males to females being 1.8:1. The mean pre-hospital duration of illness was 2 weeks; the mean time to diagnosis after admission was six days. We noted that patients who died had a shorter pre-hospital duration of illness of 4–7 days.

Fever was the commonest symptom at presentation (59%), followed by pleuritic chest pain (29.4%) and shortness of breath (23.5%). Loss of appetite (13.8%), night sweats (7.8%) and headache (7.8%) ranked next. Lethargy (4%) was less common. Two patients with a history of intravenous drug abuse presented with neck pain, one due to a retropharyngeal abscess and the other due to a cervical epidural abscess. In this series, intravenous drug abuse was the commonest risk factor, followed by valvular heart disease. HIV, although not an independent risk factor, occurred in 17.6% of cases. Interestingly, intravenous drug abuse was more prevalent during 1987–1991 (45%) than during 1992–1997 (13.7%), although the numbers are too small to be statistically significant. A previous history of endocarditis was given by 15.6% of patients. Only one patient had a congenital heart lesion, a univentricular anomaly.

The commonest organism was *Staphylococcus aureus* (43%) followed by alpha hemolytic *Streptococci* (13.7%). *Staphylococcus epidermidis* was seen in 6%, *Pseudomonas aeruginosa* in 6%, *Streptococcus pneumoniae* in 6%, *Streptococcus faecalis* in 6%, *Escherichia coli* in 2% and *Klebsiella pneumoniae* in 2%; 13.7% of cases were culture negative.

Septic emboli occurred in 12 patients (23%); the commonest site was to the lungs (9.8%). Two patients had intracranial mycotic aneurysms complicated by subarachnoid hemorrhage. One had emergency resection. Both however died. One of the patients had emboli to the brain, liver and lungs and died. Emergency aortic valve replacement for vegetation-induced acute aortic incompetence was performed in one patient and another had surgery for cord compression secondary to epidural abscess. In all, 3 patients (5.9%) needed emergent surgery.

No patients in this series gave a history of a recent dental procedure. In our series, the incidence of hematuria was 10% (compared to previous reports of 49% to 70%). Thirty-two patients (62.3%) had valvular vegetations. The tricuspid valve was involved in 46.8%, followed by mitral valve 31.2%.

There was an overall mortality of 13.7% with a decrease in mortality from 15.6% in the first five years to 10.5% in the latter six years of the study. Cause of death was congestive heart failure in four patients (7.8%), subarachnoid hemorrhage secondary to mycotic aneurysm in two patients (3.9%), multiple emboli to brain, liver and lungs with sepsis in one patient (1.9%).

Summary And Conclusions: There was a higher incidence of endocarditis among males, the commonest presenting symptom was fever, the commonest organism *S. aureus* and septic emboli were the most frequent complication. Unlike other studies in which the aortic valve was the most frequently involved (2) in our series the tricuspid valve was more often involved. We had a very low incidence of surgery, low incidence of hematuria and no patients had previous dental procedures. Our overall mortality is significantly lower than any other series (21–35%) (3, 5) and may be explained on the basis of a higher frequency of intravenous drug abusers and right-sided endocarditis which is known to have a better outcome. The lower mortality in the latter half can be accounted for at least in part to earlier diagnosis and treatment and the use of transesophageal echocardiography which was commenced in 1992 at Queens Hospital Center.

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Short-Term Effect of Phentermine and Fenfluramine on Weight and Lipid Profiles in Obese Individuals. I. Sachmechi, K. Kakzawa, A. Srivastava, and L. Rezainadimi. Department of Medicine, Division of Endocrinology, Mount Sinai Services at Queens Hospital Center, Jamaica, NY.

Objective: To evaluate the short-term effect of the combination of phentermine and fenfluramine on weight and lipid profiles in obese individuals.

Methods: Thirty-seven patients (35 female, 2 male) were enrolled with eligibility criteria including: age 20–59 years; 20% over desirable body weight or body mass index ≥ 28, no serious medical or psychiatric disease, and no contraindications to drug therapy. Patients were instructed on diet, exercise, and behavior modification techniques and received phentermine (15 mg/day) and fenfluramine (60 mg/day) continuously for 6 months. Nine patients dropped out of the study (3 for significant increase in blood pressure, 2 for gastrointestinal upset, 2 for complaints of memory clouding, one for chest pain, and one with new onset diabetes).

Results: Mean average weight reduction in the 28 patients who completed the study was 29.53 lbs. ($p=0.0153$), or 12.84% of initial body weight. Mean body mass index decreased by 4.607 ($p=0.0046$). The total cholesterol decreased from a mean of 237.14 ± 34.03 (mg/dL) to 204.61 ± 27.345 (mg/dL) for a mean reduction of 32.53 or 13.7% ($p=0.0002$). The total serum triglycerides decreased from a mean of 203.32 ± 96.62 (mg/dL) to 156.93 ± 65.55 mean reduction of 46.39 or 22.81%. The LDL cholesterol decreased from the mean of 153.04 ± 37.25 (mg/dL) to 127.93 ± 25.84 (mg/dL) for a mean reduction of 25.10 or 16.4%. Total mean serum HDL cholesterol increased from 40.96 ± 16.41 (mg/dL) to 47.00 ± 16.96 (mg/dL) for a mean increase of 6.03 or 14.72%.

Conclusion: Diet therapy with the combination of phentermine and fenfluramine significantly reduces weight and improves the lipid profile in obese patients. The improvement in lipid profile was much more than expected due to weight reduction alone, suggesting the possibility that phentermine and/or fenfluramine may have a direct effect on the production or clearance of lipoproteins. This study was done in 1995 when phen/fen was approved by the FDA.

Hepatic Nodular Sarcoidosis Mimicking Disseminated Cancer. G. Shidham, M. Sharma, A. Briones, T. Otrok, D. Sondhi, S. Chokhavatia, and F. Rosner. Department of Medicine, Mount Sinai Services at Queens Hospital Center, Jamaica, NY and Mount Sinai School of Medicine, New York, NY.

Introduction: Most patients with sarcoidosis are diagnosed between 20 and 40 years of age. The disease is very rare among Southeast Asians. Thoracic sarcoidosis commonly presents with characteristic radiographic and computed tomographic (CT) findings of interstitial lung disease and mediastinal/hilar lymphadenopathy. In contrast, CT findings of abdominal sarcoidosis are less characteristic and are commonly reported as nonspecific hepatosplenomegaly, retroperitoneal lymphadenopathy and, least commonly, hepatosplenic nodules. These nodules may occur in one of five patterns of which hepatic predominance is the least common presentation. The hepatosplenic nodular appearance can be mistaken for lymphoma, metastatic cancer or infection.

Case Study: A 58-year-old Asian Indian woman had a 6-month history of abdominal pain, nonproductive cough, loss of appetite, low grade fever and weight loss. On physical examination, the liver was enlarged (17 cm), as was the spleen (5 cm below the costal margin). No lymphadenopathy was noted. Laboratory data showed aspartate transaminase of 114 IU/L (normal: 2–40), alanine transaminase of 75 IU/L (normal: 2–50), alkaline phosphatase of 690 IU/L (normal: 30–115) and angiotensin converting enzyme of 86.7 units/L (normal: 8–52). Bilateral interstitial infiltrates were seen on chest X-ray. CT of the abdomen demonstrated hepatosplenomegaly with a nodular contour of the liver and multiple hepatosplenic nodular lesions with hepatic predominance. Initial diagnostic considerations were lymphoproliferative disorder, metastatic cancer and chronic granulomatous infection. Sputum, transbronchial biopsy and liver biopsy were negative for acid-fast bacilli (AFB)/fungus stains and cultures. Multiple noncaseating granulomas consistent with sarcoidosis were seen on liver and transbronchial biopsy. This elderly Asian Indian woman represents a very rare case of sarcoidosis in view of her ethnicity and hepatosplenic nodular appearance mimicking metastatic cancer.

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